Pediatrics

VOLUME 8 NOVEMBER 1951 NUMBER 5

ORIGINAL ARTICLES

EFFECT OF ADRENOCORTICOTROPHIC HORMONE ON RHEUMATIC FEVER

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THE discovery by Hench, Kendall and co-workers[1, 2] of the striking effect of cortisone on rheumatoid arthritis and acute rheumatic fever suggested that an important advance in both the treatment and understanding of diseases of connective tissue had been made. It became clear from the experiences of the present investigators and a number of personal communications (some of which have now been published[3, 4]) that a reproducible repression of the signs and symptoms of rheumatoid arthritis and rheumatic fever resulted from the administration of sufficient doses of cortisone acetate (Cortone®) or adrenocorticotrophic hormone (Acthar®).

The critical evaluation of effective therapy of rheumatic fever has always been a subject of controversy. After many years of experience in the use of salicylate there is still no complete agreement as to its therapeutic value. This difficulty is due to the great variation in manifestations, severity, duration and after-effects of this disease. It seemed of great importance from both a theoretical and practical standpoint to attempt to answer the following questions:

1. Do ACTH and cortisone repress only manifestations of the disease such as arthritis and fever, or do they also affect carditis?

2. Do ACTH and cortisone therapy affect the natural course of the disease, or do they merely suppress its manifestations while being administered?

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Supported by grants from the Chicago Heart Association and from the National Heart Institute, of the National Institutes of Health, Public Health Service. Part of the ACTH used in this study was obtained through the courtesy of Dr. John R. Mote of Armour Laboratories.

(Received for publication Feb. 9, 1951.)

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3. Does treatment of active rheumatic fever alter the development of valvular deformities?

In view of the wide variability of this disease answers to the first two questions could only be obtained either by a statistical study including a relatively large series of patients with active rheumatic fever divided into treated and control groups or by a smaller group of patients whose rheumatic activity was of sufficiently long duration as to make spontaneous remission unlikely. The question of the effect of treatment with these hormones on the occurrence of valvular disease must await a much longer follow-up period than has yet been possible.

The purpose of this paper is to report the results obtained in a relatively small series of cases (22) of various types of active rheumatic fever. These cases have consisted of patients with objective evidence of carditis who either had chronic activity (in excess of three months) or pancarditis of a severe variety. Brief summaries of the clinical history of these patients are included in this publication.

TABLE 1

Type of Rheumatic Fever	No. of Cases	No. of Cases with Previous Attacks of Rheumatic Fever
Acute	3	0
Acute with Pancarditis	8	5
Chronic	11	4

Method of Study

Selection of Patients: The 22 patients included in this study were all children ranging in age from 3½ to 15 years of age. There were 9 males and 13 females. They all had elevated sedimentation rates and signs of carditis, and there was sufficient evidence of rheumatic activity to make the diagnosis reasonably certain. As a minimum they all conformed to the Jones criteria.[5] A summary of the type of cases treated may be seen in table 1.

Clinical Management: All patients were on bedrest during the period of study and for at least one month after the study had been completed. Pulse and respiration rates and rectal temperature were recorded every four hours day and night. Blood pressure and weight determinations were made daily and the daily urinary intake and output were measured. All patients received penicillin 250,000 u. by mouth daily in an attempt to prevent intercurrent streptococcal infections. Many of the patients studied were the subject of a number of auxiliary investigations which will be recorded in later communications. The majority of the patients in this study who had evidence of chronic activity were observed carefully for a control period during which placebo injections of physiologic saline were substituted for ACTH. Potassium chloride 2.4 gm./day was administered during the period of therapy to most of the patients. Dietary sodium chloride was restricted in all patients with severe heart disease. A post-treatment control period was carried out following therapy. All patients have been under follow-up observation since discontinuation of therapy.

Laboratory Tests: Complete blood counts and sedimentation rates were determined three times a week during the period of therapy and for some time after therapy was discon-

tinued. Sedimentation rates were done by the Wintrobe method and were not corrected for anemia. Eosinophil counts were done according to the method of Randolph[6] at least once a week or more if indicated. Urinalyses and electrocardiograms were done weekly. Chest roentgenograms were taken once a week on almost all patients. Cardiac size was measured by the planimeter method. Blood was drawn at least once weekly for chemical determinations.

Administration of Drug: All patients received ACTH (Acthar®) with the exception of Patient 17, who received cortisone. The total daily dose was given intramuscularly in four equally divided doses every six hours. The majority of the patients received a course of 4 to 6 weeks of drug therapy. Therapy was generally started at 80 mg./day and cut to 40 mg. after two days. It was kept at this level for most of the experimental period and finally decreased further before stopping.

Summaries of Patients

Patient 1, K. F., a 10 yr. old boy, had chronically active rheumatic fever for 7 mo. Heart was 110% oversize and there was evidence of mitral valve stenosis and insufficiency with moderate congestive failure. He received ACTH for 30 days. During period of therapy, temperature and ESR returned to normal and heart diminished in size. Signs of congestive failure increased so markedly during the early period of therapy that ACTH had to be withheld for a few days. These signs gradually cleared during the latter period of therapy and have not since recurred. Withdrawal of ACTH was followed by a transient exacerbation of signs and symptoms of rheumatic activity followed by a gradual disappearance of evidence of activity. Fourteen months after therapy heart is 45% oversize, murmurs are still present, ESR is normal and patient is asymptomatic on limited physical activity.

Patient 2, I. B., a 10 yr. old girl, had chronically active rheumatic fever for 18 mo. with several episodes of severe congestive failure during this time. Pericarditis, mitral valve stenosis and insufficiency, 142% increase in cardiac size, moderate congestive failure, erythema annulare and subcutaneous nodules were present. She received ACTH for 32 days. During period of therapy, pericardial friction rub disappeared, murmurs diminished in intensity, and heart diminished in size. The temperature and ESR returned to normal; PR was slightly reduced and signs of congestive failure increased at first but gradually disappeared towards the end of the period of therapy. Erythema annulare recurred at frequent intervals during period of therapy. Withdrawal of ACTH was followed by a transient return of all signs of rheumatic activity present before treatment except for congestive failure and rheumatic nodules. There has been a gradual subsidence of these signs during the past 9 mo. Heart is now 83% oversize, murmurs are unchanged, ESR is normal, but a mild tachycardia and intermittent erythema annulare persist.

Patient 3, C. W., a 13 yr. old girl, had had 2 previous attacks of rheumatic fever. She had chronically active rheumatic fever for 7 mo. with pericarditis, mitral valve stenosis and insufficiency, a 110% increase in cardiac size and a gallop rhythm. She received ACTH for 38 days. During therapy the pericardial friction rub disappeared, murmurs diminished in intensity, turbulence of the cardiac action decreased and heart diminished in size. Temperature and ESR returned to normal. Withdrawal of ACTH was followed by a transient return of signs of rheumatic activity although not to the degree noted before treatment. Pericardial friction rub did not recur. There has been a gradual disappearance in the signs of rheumatic activity during past 11 mo. At present, heart is 60% oversize, murmurs are still present, ESR is normal and patient is asymptomatic on full physical activity.

Patient 4, R. K., an 11 yr. old girl, had chronic rheumatic fever for 8 mo. Mitral valve stenosis and insufficiency, aortic valve insufficiency, 90% increase in cardiac size, a gallop rhythm and mild congestive failure were present. She received ACTH for 34 days. During period of therapy the pericardial friction rub disappeared, mitral murmurs diminished in intensity, but aortic diastolic murmur became louder, P-R interval returned to normal and heart decreased in size. Temperature, PR and ESR returned to normal. Withdrawal of ACTH was followed by a return of all signs of rheumatic activity present before treatment including pericardial friction rub and an increase in cardiac size to 71% oversize. Two months after therapy pericardial friction rub had disappeared and ESR had returned to normal. Five months after therapy: tachycardia, a hyperactive heart, a systolic

hypertension, a palpable thyroid, sweaty palms, normal ESR and an increase in protein-bound iodine suggest that patient has developed mild juvenile hyperthyroidism and that the rheumatic activity probably has subsided.

Patient 5, R. S., a 10 yr. old boy, had chronic cyclic rheumatic fever for 5 yr., the last exacerbation being 18 mo. before admission. Pericarditis, mitral valve stenosis and insufficiency, a 144% increase in cardiac size and mild congestive failure were present. He received ACTH for 45 days. During period of therapy, signs of congestive failure increased at first and then gradually cleared and have not returned, pericardial friction rub disappeared, mitral systolic murmur diminished in intensity, cardiac tones were of better quality, heart diminished slightly in size and temperature and ESR returned to normal. Withdrawal of ACTH was followed by a transient return of signs of increased rheumatic activity but friction rub did not return. Two months after therapy, an episode of chills and fever and a petechial rash subsided following large doses of penicillin. Five months after therapy there has been gradual diminution in signs of rheumatic activity. ESR is normal, heart is 100% oversize, mitral murmurs persist and a mild tachycardia is still present.

Patient 6, W. W., a 9 yr. old boy, had chronic rheumatic fever for 30 mo. Mitral valve stenosis and insufficiency and a 110% increase in cardiac size were present. He received ACTH for 47 days. During period of therapy signs of congestive failure increased so markedly that ACTH had to be withheld on one occasion, an aortic diastolic murmur developed, temperature returned to normal, tachycardia decreased, but there was no change in character of murmurs, in cardiac size or in ESR. Following withdrawal of ACTH a transient increase in signs of rheumatic activity occurred. Four months after therapy, a probable friction rub was heard. Five months after therapy, tachycardia persists, there has been no change in mitral murmurs or cardiac size and ESR is normal.

Patient 7, R. M., a 6 yr. old boy, had chronic rheumatic fever for 3 mo. Mitral valve insufficiency, a heart 35% oversize and rheumatic nodules were present. He received ACTH for 33 days. During period of therapy, mitral systolic murmur diminished in intensity and ESR fell to normal, but heart increased in size. Following withdrawal of ACTH, there was a transient return of previous signs of rheumatic activity. Six months after therapy, mitral systolic murmur persists unchanged, heart is 25% oversize, ESR is normal and patient is doing well on limited physical activity.

Patient 8, A. B., a 14 yr. old girl, had first attack of rheumatic fever with some manifestations suggestive of rheumatoid arthritis 30 mo. before admission. She had had chronic rheumatic fever for 3 mo. before admission. Mitral valve insufficiency, a 31% increase in cardiac size, mild congestive failure, chorea, rheumatic nodules, and fusiform swelling of proximal interphalangeal joints were present. She received ACTH for 41 days. During period of therapy, there was no change in mitral murmur or heart size, rheumatic nodules disappeared, stiffness of fingers and swelling of proximal interphalangeal joints disappeared, signs of congestive failure gradually disappeared and temperature, respiratory rate and ESR returned to normal. Following withdrawal of ACTH, there was a transient increase in PR, respiratory rate and ESR. Four months after therapy there is a decrease in intensity of mitral murmur, no change in cardiac size, and ESR is normal. There is no evidence of rheumatic activity.

Patient 9, K. M., a 3½ yr. old girl, had chronic rheumatic fever for 8 mo. Mitral valve insufficiency, anemia, spiking temperatures, joint pains and erythema annulare were present. She received ACTH for 42 days. During period of therapy, temperature, ESR and RBC count returned to normal, tachycardia diminished, joint pains and skin rashes disappeared, and there was some fluid retention necessitating reduction of dosage of drug. Withdrawal of ACTH was followed by a return of tachycardia, anemia and elevated ESR, and a moderate increase in temperature. Two months after therapy, patient is afebrile and ESR is returning towards normal but mitral systolic murmur, tachycardia and anemia persist.

Patient 10, I. D., a 13 yr. old girl, had first attack of rheumatic fever 24 mo. before admission. She had had chronic rheumatic fever for 3 mo. before admission. Mitral valve stenosis and insufficiency, aortic valve insufficiency and a 25% increase in cardiac size were present. She received ACTH for 45 days. During period of therapy, there was no change in mitral murmurs, aortic diastolic murmur became louder, cardiac size was unchanged, tachycardia diminished and ESR returned to normal. Following withdrawal of ACTH, there was a transient increase in PR and ESR. Six weeks after therapy PR and ESR are normal, aortic diastolic murmur has disappeared, there has been no change in mitral murmurs or heart size and patient is doing well on limited physical activity.

Patient 11, M. K., a 13 yr. old girl, had chronic rheumatic fever for 4 mo. Mitral systolic and diastolic murmurs, aortic diastolic murmurs, a 35% increase in cardiac size, a temperature rising to 39°C. daily, and mild congestive failure were present. She received ACTH for 15 days. ACTH had no beneficial effect on course of her disease and signs of congestive failure increased to such an extent that drug had to be withdrawn. Patient became progressively worse during next 8 days and died in spite of receiving large doses of cortisone during last 3 days of life.

Patient 12, P. R., a 13 yr. old boy, had had 2 previous attacks of rheumatic fever. Present attack started 1 wk. before admission. Cyanosis, acute respiratory distress, mitral systolic and aortic diastolic murmurs, a 100% increase in cardiac size, pericarditis, anemia, albuminuria and microscopic hematuria were present. He received ACTH for 52 days. During period of therapy, pericardial friction rub disappeared, cardiac sounds were of better quality, murmurs diminished in intensity, cardiac size decreased, signs of congestive failure gradually cleared, temperature and ESR fell to normal, but there was no change in the anemia or urinary findings. Withdrawal of ACTH was followed by transient increases in temperature, PR and ESR. Six months after therapy, murmurs are unchanged, heart remains 35% oversize, urinary findings and anemia have cleared, ESR is normal and the patient has no evidence of rheumatic activity.

Patient 13, E. W., a 10 yr. old boy, had first attack of rheumatic fever 2 wk. before admission. Dyspnea, orthopnea, a mitral systolic murmur, pericarditis, a 100% increase in cardiac size and severe congestive failure were present. He received ACTH for 42 days. During period of therapy, pericardial friction rub disappeared, cardiac tones improved in quality, heart diminished in size, but mitral murmur and elevated ESR persisted. During 5th wk. of therapy, there was a transient increase in cardiac size and an increase in temperature and PR. Withdrawal of ACTH was followed by a transient increase in PR. ESR gradually fell to normal. Five months after therapy, apical systolic murmur has disappeared, heart is normal in size and patient has no evidence of rheumatic activity.

Patient 14, A. L., an 8 yr. old girl, had 2 previous attacks of rheumatic fever. Present attack started 2 wk. before admission. Dyspnea, pericarditis, mitral systolic and diastolic murmurs, a 75% increase in cardiac size, anemia and severe congestive failure were present. She received ACTH for 44 days. During period of therapy, pericardial friction rub disappeared, cardiac tones improved in quality, heart diminished in size, signs of congestive failure gradually cleared, temperature, PR and ESR fell to normal, and anemia disappeared. Following withdrawal of ACTH, there was an increase in temperature, PR and ESR with a gradual return to normal during next 2 mo. Four months after therapy, apical diastolic murmur has disappeared, apical systolic murmur persists, heart is 30% oversize, ECG has returned to normal, but a mild tachycardia and occasional temperatures to 38°C. persist.

Patient 15, B.W., a 7 yr. old boy, had first attack of rheumatic fever 1 mo. before admission. Dyspnea, pericarditis, mitral systolic and diastolic murmurs, a heart 85% oversize, temperature of 40.5°C., erythema annulare, rheumatic nodules and moderate congestive failure were present. He received cortisone for 21 days. During period of therapy, pericardial friction rub disappeared and temperature and ESR returned to normal, but there was no improvement in cardiac tones, heart enlarged further, gallop rhythm, dyspnea and tachycardia persisted, and signs of congestive failure became more marked. Withdrawal of cortisone was followed by an increase in tachycardia and dyspnea, a return of pericardial friction rub and a rise in ESR. Patient then received ACTH for 59 days. During 1st 6 wk. of ACTH he was very ill with many episodes of severe congestive failure which were difficult to control. Pericardial friction rub disappeared, cardiac tones improved in quality, heart diminished slightly in size and ESR fell to normal, but tachycardia and mitral murmurs persisted. Withdrawal of ACTH was followed by a rise in ESR and a gradual return to normal. Three months after therapy, mitral murmurs, a 70% increase in cardiac size and electrocardiographic abnormalities persist.

Patient 16, P. O., a 10 yr. old girl, had had 3 previous attacks of chorea. Present attack of rheumatic fever started 2½ wk. before admission. Marked dyspnea, cyanosis, pericarditis, mitral systolic and diastolic murmurs, anemia, temperature of 39.4°C., gross cardiac enlargement and severe congestive failure were present. ACTH was given for 5 days without any effect on patient's progressively downhill course and she died on 5th day of therapy. Postmortem examination showed acute rheumatic pancarditis and rheumatic pneumonitis.

Patient 17, G. B., a 13 yr. old boy, had had one previous attack of rheumatic fever. Present

attack started 2 wk. before admission. Dyspnea, pericarditis, mitral systolic and diastolic murmurs, an aortic diastolic murmur, gross cardiac enlargement and severe congestive failure were present. In spite of receiving 300 mg. of cortisone, he continued to run a progressively downhill course and died 36 hr. after admission. Postmortem examination showed acute rheumatic pancarditis and rheumatic pneumonitis.

Patient 18, M. W., a 9 yr. old boy, had first attack of rheumatic fever 3½ wk. before admission. Dyspnea, pericarditis, apical systolic and diastolic murmurs, and an aortic diastolic murmur, a 37% increase in cardiac size, anemia and severe congestive failure were present. He received ACTH for 39 days. Congestive failure increased so markedly during early period of therapy that ACTH had to be withheld for 4 days. Following resumption of therapy, congestive failure gradually cleared, pericardial friction rub disappeared, cardiac tones improved in quality, aortic systolic and mitral diastolic murmurs disappeared, heart decreased in size, ESR returned to normal, anemia cleared and PR diminished somewhat. Following withdrawal of ACTH, ESR rose but fell again to normal. One month after therapy, cardiac tones were of poor quality, aortic systolic and apical diastolic murmurs and gallop rhythm returned, heart had increased in size, liver was moderately enlarged and there was marked tachycardia. Patient received ACTH for next 4 days. In spite of therapy, tachycardia continued, temperature rose to 39.5°C., there was a marked increase in respiratory rate, liver enlarged further in spite of digitalization and diuretics, anuria developed and patient died during 4th day of therapy. Postmortem examination showed subsiding acute pericarditis and acute rheumatic myocarditis with mitral valvulitis and insufficiency.

Patient 19, N. R., a 5 yr. old girl, had had one previous attack of rheumatic fever. Present attack started 7 mo. before admission with a sudden increase in severity of signs and symptoms following a sore throat 5 days before admission. Dyspnea, cyanosis, mitral systolic and diastolic murmurs, gross cardiac enlargement, temperature of 39.2°C., and moderate congestive failure were present. ACTH was given for 4 days. In spite of all therapeutic measures, patient continued to run a progressively downhill course and died on 4th day of therapy. Postmortem examination showed acute rheumatic pancarditis.

Patient 20, J. O., a 4 yr. old girl, had first attack of rheumatic fever starting 6 wk. before admission. Mitral systolic and presystolic murmurs, a heart normal in size, a low grade fever, tachycardia, some anemia and mild congestive failure were present. She received ACTH for 44 days. During period of therapy there was a decrease in PR, temperature returned to normal, cardiac tones inproved in quality, gallop rhythm disappeared, apical presystolic murmur diminished in intensity, signs of congestive failure disappeared and ESR fell to normal. Following withdrawal of ACTH, there was a return of low grade fever, tachycardia, anemia and gallop rhythm; heart again sounded overactive and presystolic murmur became more prominent. There was a transient rise in ESR and a gradual return to normal. Three months after therapy, tachycardia persists and heart still sounds overactive.

Patient 21, P. W., a 9 yr. old girl, had first attack of rheumatic fever 4 days before admission. An apical systolic murmur, a normal sized heart, a low grade fever and tachycardia were present. Six weeks after onset of disease, patient was treated with ACTH for 41 days. During period of therapy, there was no change in murmur or tachycardia, ESR returned to normal. Withdrawal of ACTH was followed by a transitory rise in ESR, and a return of low grade fever. Six weeks after therapy, PR had returned to normal, apical systolic murmur had diminished in intensity and patient showed no signs of rheumatic activity. Three months after therapy, patient is asymptomatic on full physical activity.

Patient 22, P. M., a 6 yr. old girl, had first attack of rheumatic fever 2 wk. before admission An apical systolic murmur, a normal sized heart, low grade fever and tachycardia were present. She received ACTH for 20 days. During period of therapy, temperature became normal, PR slowed, ESR fell to normal and P-R interval diminished, but there was no change in apical systolic murmur. On 20th day of therapy, patient developed status epilepticus for 3 hr. Lumbar puncture revealed a high spinal fluid protein. Four days later patient was again rational. Neurologic examination was negative until 3 wk. after convulsive seizures when hyperactive deep reflexes of knees and ankles were noted. Following withdrawal of ACTH there was a transient increase in ESR, temperature and PR. Three months after therapy, although sleeping PR remains at 70 and ESR is normal, temperature continues to rise occasionally to 38°C. There is no change in apical systolic murmur and heart has enlarged slightly.

Discussion

It is to be expected that different results of therapy might be obtained in different groups of patients. Although it is difficult to classify rheumatic fever into types of disease because there is a continuous series of intermediates, it may nevertheless be of value to consider the results of therapy in terms of various types of patients.

Several reports[2-4] have appeared concerning the effect of ACTH and cortisone therapy on patients with first attacks of rheumatic fever, with and without evidence of carditis. In general the results have indicated relatively uniform success in the repression of all manifestations of disease in these patients. The course after withdrawal of the drug has been less uniform. Many patients show some evidence of reactivation which frequently subsides spontaneously. It is difficult to determine whether this rebound phenomenon is due to the fact that the disease has been only repressed during therapy, or that there is a depression of pituitary or adrenal function during administration, which results in deficiency upon withdrawal.

Chart 1 represents the response to therapy of Patient 13 who had evidence of acute

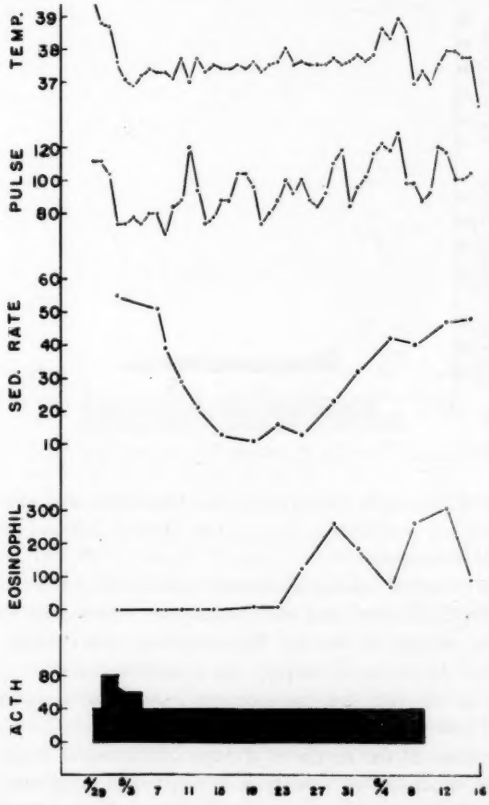

Chart 1. Effect of ACTH therapy on patient with acute pancarditis.

pancarditis. This patient had a striking immediate response to therapy and was markedly improved in a short period of time. It should be remembered, however, that a certain number of patients with acute pancarditis respond well to conventional forms of therapy. Patients 12, 14 and 18 showed similar responses but Patients 16, 17 and 19 were apparently unaffected by therapy. The reasons for differences in response in these patients are not at present clear.

Chart 2 illustrates the course of a chronically active patient (3) who had a striking

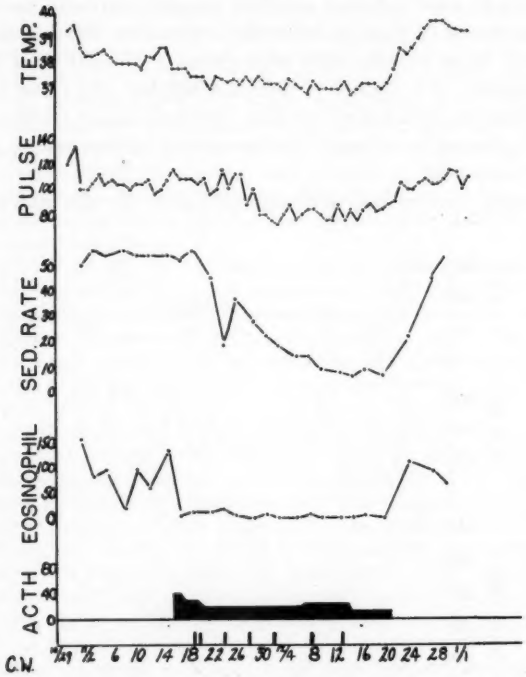

CHART 2. Effect of ACTH therapy on patient with chronically active rheumatic fever.

response to therapy by all measurable criteria, but who reactivated after withdrawal. She ultimately had a complete remission of disease, but whether this was related to her course of therapy is difficult to ascertain.

Chart 3 shows the course of another chronically active patient (5) who had a somewhat less striking response to therapy, and withdrawal was attended by evidence of activity more severe than that previous to therapy. There has been little evidence in his subsequent course to suggest that the period of therapy has altered the disease in a striking fashion with the exception of the fact that the frequent episodes of congestive failure in the pretreatment period have not been repeated since therapy.

The critical evaluation of the results of therapy of rheumatic fever requires not only consideration of the variability of severity and duration of symptoms but a differential consideration of the various manifestations of this disease. If one considers the rheumatic process as a generalized inflammatory reaction affecting particularly connective tissue, one

might consider the various clinical manifestations of the disease as a unit representing the total inflammatory process. It is the peculiar character of this disease, however, that certain manifestations are self-limited while others persist over long periods of time and result in permanent tissue damage. Thus the arthritis of rheumatic fever rarely occurs except early in the disease, while evidences of active carditis may persist for many years.

In attempting to gain an understanding of the changes produced in this group of patients, the authors have analyzed separately various manifestations.

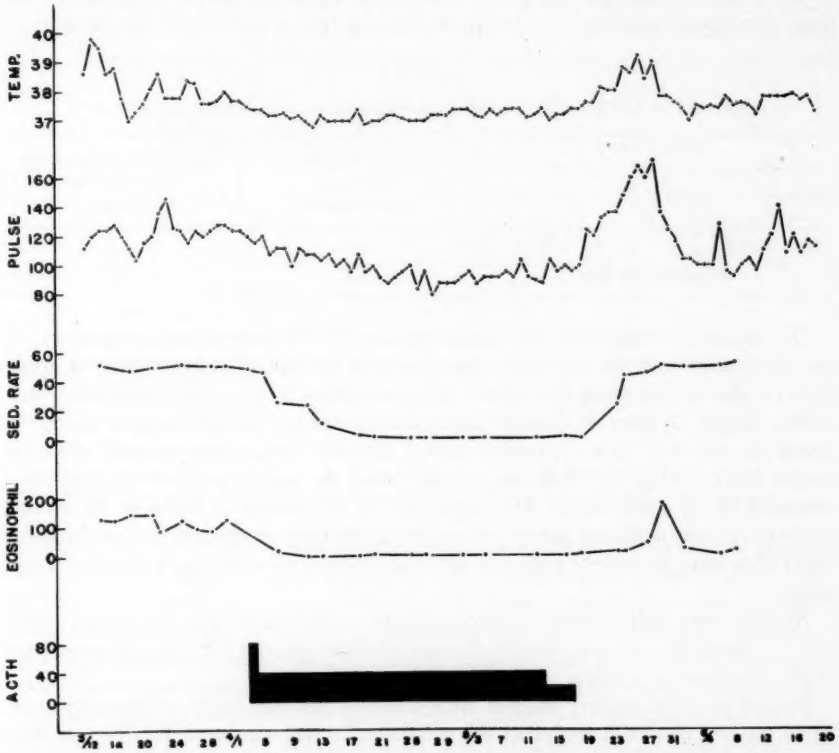

CHART 3. Effect of ACTH therapy on patient with chronically active rheumatic fever.

The effect of ACTH and cortisone therapy on arthritis has been reported by Hench et al.,[2] Barnes[7] and Massell.[3] These workers have all found a striking diminution in arthritis. Although there is little reason to doubt that these effects have been due to hormone therapy, it should be remembered that the polyarthritis of acute rheumatic fever responds strikingly to salicylate therapy and frequently to bedrest. In the present authors' series arthritis was so infrequent an occurrence as to make evaluation of therapy impossible.

Elevation of temperature is a prominent feature of acute attacks of rheumatic fever. In chronic stages it is a less regular occurrence although it was present with a high frequency in this series of cases. In a number of the cases the elevation of temperature was minimal so that previous to therapy there was some question of interpretation. The change that

occurred in these cases after institution of therapy was sufficiently striking so as to leave little doubt as to effects on temperature.

Table 2 shows the effect of therapy on fever. Nineteen of the 22 patients showed a significant elevation of temperature immediately preceding therapy. Only three of these showed no definite diminution of fever during therapy, all of these belonging to the group of patients with pancarditis who died while under therapy. A fourth patient, who is listed with those responding, failed to respond during a succeeding episode of disease to which he succumbed. Several patients had febrile episodes while receiving therapy but these were always associated with small doses of the drug or intercurrent infections.

TABLE 2

EFFECTS OF ACTH ON FEVER AND SEDIMENTATION RATE IN RHEUMATIC FEVER

	Total Patients Showing Manifestations	Patients' Manifestations Decreased by Therapy
Fever	19	16
Sedimentation Rate	22	18

The incidence of rheumatic skin rashes (typical erythema marginatum and annulare) in this series of patients was too low to draw any final conclusions as to the effect of drugs. Four patients in this series had typical rheumatic rashes in the period immediately preceding therapy. In three of these the rashes disappeared and did not reappear during the course of treatment. In one patient a typical erythema marginatum occurred while the patient was receiving ACTH during a period when she was judged to have an excellent remission by all other criteria. The importance of this finding in terms of the over-all rheumatic process is difficult to interpret in view of the frequent observation that rheumatic skin rashes occur in patients long after all other evidence of rheumatic activity has disappeared.

Nodules were only present in three patients of this series and disappeared in all patients during the course of therapy. In none of these cases did they reappear subsequent to the withdrawal of therapy.

Possibly the most uniform effect of ACTH therapy has been on the sedimentation rate. In all patients treated in this series the sedimentation rate was markedly elevated. With exception of the patients who died during therapy, a striking decrease in sedimentation rate was observed. The time required for the return of the sedimentation rate to normal was somewhat variable, but in general varied between 10 and 14 days. This measurement was the most convenient index for following patients and in general correlated well with clinical remissions. It was noted that many of the patients under therapy showed sedimentation rates below those usually seen in normal children. Similar observations have been made on patients with syndromes other than rheumatic fever. This raises the question whether these drugs exert some nonspecific effect on the sedimentation rate thus vitiating the use of this measurement as an index of remission in rheumatic patients. However, on several occasions elevated sedimentation rates were observed in other diseases which failed to respond to ACTH therapy. Further study of the effects of ACTH and cortisone therapy on the sedimentation rates of normals and patients with a variety of

diseases would seem necessary before a definite answer to this question can be given. Although these drugs may depress the sedimentation rate nonspecifically this measurement may still parallel remission and thus be of value in following drug effects.

At the outset of this study it seemed that one of the major questions to be answered was whether ACTH therapy suppresses the inflammatory reaction which occurs in the heart in rheumatic fever. It was for this reason that almost all patients selected for this study were ones who had evidence of important cardiac involvement.

Table 3 lists the various manifestations of carditis and the changes which occurred during therapy. It is obvious that selection of patients with maximum evidence of carditis also involves selection of a certain number of patients with structural cardiac damage

TABLE 3

EFFECT OF ACTH ON MANIFESTATIONS OF CARDIAC INVOLVEMENT

	Total Patients Showing Manifestations	Patients' Manifestations Decreased by Therapy
Apical Systolic Murmur	22	1
Apical Diastolic Murmur	15	0
Aortic Diastolic Murmur	6	0*
Pericardial Friction Rub	10	7
Tachycardia	22	17
Cardiac Enlargement	17	8
Congestive Failure	13	10
Prolonged P-R Interval	10	4

* Three patients exhibited increased evidence of aortic valve regurgitation during therapy.

which could hardly be expected to be reversed during therapy. This is particularly true of evidence of valvular disease as exhibited by the presence of murmurs. As is seen in table 3 there was little change in the presence of murmurs heard in this group of patients. The analysis in terms of complete disappearance of murmurs does not, however, give a true picture of the actual changes, since in many of these patients there was a marked decrease in the intensity of murmurs, particularly the mitral systolic murmurs. Aortic diastolic murmurs actually became more intense in several of these patients, but this was at least partly an artifact due to decreased rate and turbulence of heart sounds which made aortic diastolic murmurs more easily audible. Sea gull murmurs were present in a number of patients and uniformly disappeared before the course of therapy was discontinued although in some cases they became more intense or appeared during therapy before disappearing.

One of the most striking changes on carditis was the uniform disappearance of pericardial friction rubs except in those patients who died during therapy. The time required for disappearance of such evidence of pericarditis varied widely in different patients, occurring in the first few days of therapy in a few, but requiring from one to two weeks in others. Significant tachycardia (resting pulse rate in excess of 100/min.) was present in all patients studied and with the exception of those patients who died, the pulse rate returned to normal during therapy. In a few patients the apparent bradycardia which has previously been described was observed.

Congestive failure was present in 13 patients of this series previous to therapy. In three patients this was accentuated during therapy, but could be controlled by mercurial diuretics and/or withdrawal of drug for brief periods of time. In 10 of the 13 cases, however, evidences of congestive failure had disappeared before the cessation of therapy. No patient of this group has had a recurrence of congestive failure subsequent to therapy.

Interpretation of electrocardiographic changes has been difficult. For purposes of summary in table 3, increased conduction time was used as the sole criteria. Only three patients of the 10 who had increased P-R intervals showed a definite and consistent change to normal. In four others there were questionable changes. Many patients of this series showed numerous T wave and S-T segment changes before therapy. Interpretation of these changes is difficult, but in general there was little evidence of consistent changes toward normal. Preliminary detailed analyses of these electrocardiograms suggests that some S-T segment and T wave changes may have been induced by therapy. Whether these are a result of electrolyte shifts (not reflected in serum analyses) requires further study.

Unequivocal evidence of cardiac enlargement was present in 17 cases of this series. In eight of these cases definite decrease in cardiac size occurred during the course of therapy. Decrease in cardiac size was considered definite when this amounted to at least 25% without correction for body weight. The marked weight changes of patients receiving ACTH therapy results in bizarre effects in cardiac size if nomograms depending on weight are used.

The changes observed in the various manifestations of carditis suggests that ACTH therapy exerts a definite effect on carditis.

The problem of whether ACTH therapy in any way changes the natural history of rheumatic fever is somewhat more difficult of soultion. It is striking that no patient in this series has had evidence of congestive failure at any time following the course of ACTH therapy. This might be taken to mean that ACTH therapy has in some way interrupted the long period of activity in some of these patients. It is apparent, however, that such an interpretation is open to pitfalls, in that the total period involved in the pretreatment, treatment and post-treatment period is sufficiently long to make spontaneous subsidence of activity an important possibility.

In almost all patients of this series there was definite evidence of reactivation of disease upon withdrawal of drug. The intensity and duration of this reactivation was highly variable. In general the reactivation was more severe in patients with chronically active disease. Final answer to the question of the effect of ACTH therapy on the natural history of disease will require the study of a much larger number of patients.

The question as to whether treatment with ACTH might in any way alter the eventual appearance of valvular damage obviously requires a long term period of follow-up. If one views the development of valvular damage as a result of late proliferative changes following rheumatic fever (recognized or unrecognized), the inhibition of the inflammatory process during the acute phase may well be expected to result in a significant decrease in the incidence of valvular damage. If, however, one views late valvular damage as a result of long term low grade inflammatory disease, the situation appears less hopeful, unless it can be shown that rheumatic activity terminates after a course of therapy. Such reasoning can only be considered in the realm of speculation at our present state of knowledge. The final answers to these questions can only come from carefully controlled long term studies. It seems obvious that unless such studies are conducted, these not in-

nocuous drugs may be used for many years without any critical evaluation of their efficacy.

Summary

ACTH therapy represses the manifestations of active rheumatic fever including those of carditis. There is as yet no conclusive evidence as to whether ACTH therapy affects the natural course of rheumatic fever. A relatively large percentage of patients in this study showed evidence of reactivation of disease on withdrawal of drug.

As used in these studies ACTH therapy did not uniformly prevent death due to acute rheumatic pancarditis. There is no evidence to indicate whether treatment of active rheumatic fever with ACTH changes the incidence of late valvular deformities.

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Spanish Abstract

Efectos de la Hormona Adrenocorticotropica en la Fiebre Reumatica

Once pacientes con fiebre reumatica crónica activa y once pacientes con fiebre reumatica aguda fueron tratados con ACTH durante un periodo de 4 a 6 semanas. Se encontró que el tratamiento con ACTH suprime las manifestaciones de la fiebre reumatica activa, incluyendo la carditis. Se estima que aún no existe evidencia conclusiva en cuanto a si el tratamiento con ACTH modifica ó afecta el curso natural de la fiebre reumatica. Un promedio relativamente grande de los pacientes tratados en este estudio presentaron evidencia de reactivación de la enfermedad siguiente a la supresión de la droga.

El tratamiento con ACTH usado en este estudio no previno uniformemente la muerte debido a pancarditis reumatica aguda. No se encontró evidencia que indique que el tratamiento de la fiebre reumatica activa con ACTH modifique la incidencia de las deformidades valvulares ulteriores.

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INTERPRETATION OF THE BASAL METABOLIC RATE OF CHILDREN OF UNUSUAL BODY BUILD

By ALBERTA ILIFF, PH.D., VIRGINIA A. LEE, M.S., AND ROBERT C. LEWIS, PH.D.
Denver

THE interpretation of the basal metabolic rate (BMR) of children of unusual size is of particular importance since many cases of suspected endocrine dysfunction show disproportionate body build. This problem has been discussed by a number of investigators; however, they have shown considerable disagreement as to whether the best method of reference for calculating basal metabolism is one based on weight, on height, on surface area or on each of these in relation to age. This difference of opinion is not surprising, since widely divergent results are obtained when the BMR, expressed as percentage deviation from a standard, is calculated for a child of atypical body build by the use of these different methods of reference. These discrepancies have caused the test on children of unusual body build to fall into general disrepute. For these reasons an attempt has been made here to evaluate these variations by determining the relative predictive value of these six commonly used methods of reference.

PROCEDURE

Data first selected for this purpose were the results of 558 determinations of BMR on 86 healthy children of the Child Research Council between 2 and 16 yr. of age. These were children whose weight or height or both weight and height at the time the test was taken fell between the 90th and 100th percentiles or between the zero and 10th percentiles of children of similar age on whom Council standards had been established. As none of these children showed an extreme variation in body build, an analysis of 946 tests reported in the literature on 793 children between 2 and 16 yr. of age has also been made. These children, who were considered free of endocrine disturbance by their investigators, fell below the 10th percentile or above the 90th percentile of Child Research Council children either in weight or in height or in both weight and height. The children were classified according to type of body build as shown in table 1.

In order to evaluate this arbitrary selection of 6 types of body build, the weight-height ratio, $\left(\frac{\text{wt. in gm.}}{(\text{ht. in cm.})^3} \times 100\right)$, of each of the children here reported was determined and plotted against the standard values for age compiled by Boyd[1] from data obtained on Child Research Council children. It was found that values for "tall" and "short" as well as for "thin" and "obese" children differentiated into distinct areas on her graphs. This tended to substantiate the present authors' method of selection of body types. On the other hand, values for "large" and "small" children were interspersed and covered a wide range, thereby demonstrating the variation in weight-height relationships for these 2 types of body build.

All BMR were calculated from Council standards[2] so as to eliminate variations which would result from the use of standards established by different laboratories. Methods of reference used were those for calories/hr./sq. m., cal./hr./kg. and cal./hr./cm., each referred to age, and cal./hr. referred to surface area, weight and height, respectively. Since no difference in distribution was found between sexes, results on boys and girls were combined.

From the Child Research Council and the University of Colorado School of Medicine, Denver.

A preliminary report of this study was made at the meetings of the American Institute of Nutrition in Chicago, May 1947 (Iliff, Alberta, and Lewis, R. C., Fed. Proc. 6:410, 1947).

(Received for publication May 22, 1951.)

TABLE 1

METHOD OF SELECTION OF TYPES OF BODY BUILD ON BASIS OF COMPARISON WITH CHILD RESEARCH COUNCIL CHILDREN OF SIMILAR AGE

Wt.	Ht.	Referred to in text as
Below 10th percentile	Below 10th percentile	Small
Above 90th percentile	Above 90th percentile	Large
Below 10th percentile	Between 10th and 90th percentiles	Thin
Above 90th percentile	Between 10th and 90th percentiles	Obese
Between 10th and 90th percentiles	Below 10th percentile	Short
Between 10th and 90th percentiles	Above 90th percentile	Tall

RESULTS

Chart 1 gives the results found on the "small" and "large" Child Research Council children, respectively. The histograms show the percentage deviation of the basal metabolism from the Child Research Council standards.[2] The BMR has been calculated for the six methods of reference previously mentioned and is indicated on the abscissa. The solid vertical line represents the value of theoretic zero, and the broken vertical lines, the generally accepted "normal" range of minus 15 to plus 15%. The frequency is indicated on the ordinate.

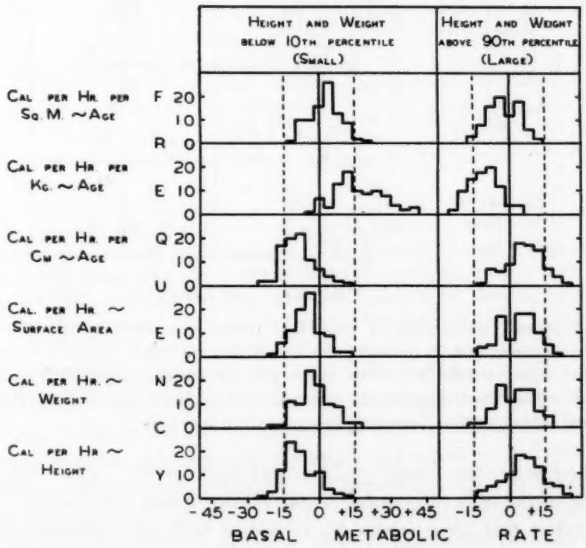
HEIGHT AND WEIGHT BELOW 10TH PERCENTILE (SMALL)
HEIGHT AND WEIGHT ABOVE 90TH PERCENTILE (LARGE)
CAL. PER HR. PER SQ. M. ~ AGE
CAL. PER HR. PER KG. ~ AGE
CAL. PER HR. PER CM ~ AGE
CAL. PER HR. ~ SURFACE AREA
CAL. PER HR. ~ WEIGHT
CAL. PER HR ~ HEIGHT
F R E Q U E N C Y
20
10
0
-45 -30 -15 0 +15 +30 +45 -15 0 +15
BASAL METABOLIC RATE

CHART 1. Frequency distribution of percentage deviation of basal metabolism, for each of 6 methods of reference indicated on ordinate, of Child Research Council children whose height and weight both fall either below 10th percentile or above 90th percentile of values for children on whom Council standards were established. Solid vertical lines represent value of theoretic zero and broken vertical lines range of minus 15 to plus 15%.

When calculated on the basis of cal./hr./sq.m. referred to age and of cal./hr. referred to surface area and to weight, respectively, more than 92% of the 88 BMR found on the "small" children and of the 85 rates on the "large" children fall within the range of minus 15 to plus 15%, and there is very little distortion. On the other hand, 52% of the BMR computed for cal./hr./kg. referred to age are higher than plus 15% for the "small" children and 32% are lower than minus 15% for the "large" children. The rates calculated for cal./hr./cm. referred to age and for cal./hr. referred to height show a

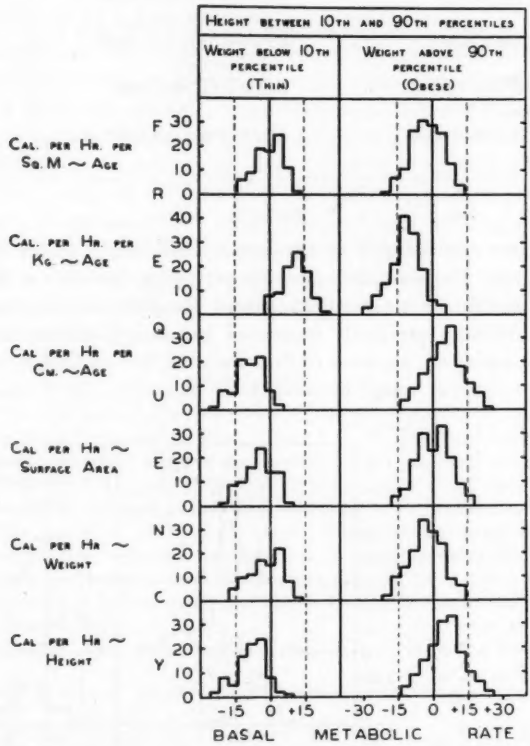
Height between 10th and 90th percentiles
Weight below 10th percentile (Thin)
Weight above 90th percentile (Obese)
Cal. per Hr. per Sq. M ~ Age
Cal. per Hr. per Kg. ~ Age
Cal per Hr per Cm. ~ Age
Cal per Hr ~ Surface Area
Cal per Hr ~ Weight
Cal per Hr ~ Height
F R E Q U E N C Y
30
20
10
0
40
-15 0 +15
-30 -15 0 +15 +30
BASAL METABOLIC RATE

CHART 2. Frequency distribution of percentage deviation of basal metabolism, for each of 6 methods of reference indicated on ordinate, of Child Research Council children whose height falls in median 80% and whose weight falls either below 10th percentile or above 90th percentile of values for children on whom Council standards were established. Solid vertical lines represent value of theoretic zero and broken vertical lines range of minus 15 to plus 15%.

tendency to be low for the "small" children and high for the "large" children, although less than 24% of the tests fall outside of the plus or minus 15% range.

It is of interest that these results are consistent with the conclusions which may be drawn from our knowledge of the nature of individual variations in body build. For example, a child who is considered "small" because of his divergence from the average range of values for height and weight at his age level would be expected to have a BMR, calculated on the basis of cal./hr./kg. referred to age, that deviates noticeably toward the high side from the standard value. However, if age as such is eliminated and the BMR

is calculated from the standards for cal./hr. referred to weight, one would expect the result to be similar to that found for an average sized child of the same age. The data charted in chart 1 show this to be true. This relationship will be discussed in more detail in a future publication.

Chart 2 gives the BMR calculated from the six methods of reference for the "thin" and "obese" Council children, respectively. When calculated on the basis of cal./hr./sq. m. referred to age and cal./hr. referred to weight, 92% or more of the BMR for the 89 tests on the "thin" children and of the 149 tests on the "obese" children are well centered within the range of minus 15 to plus 15%. This is also true for the "obese" children in the case of cal./hr. referred to surface area, but there is distortion to the negative side

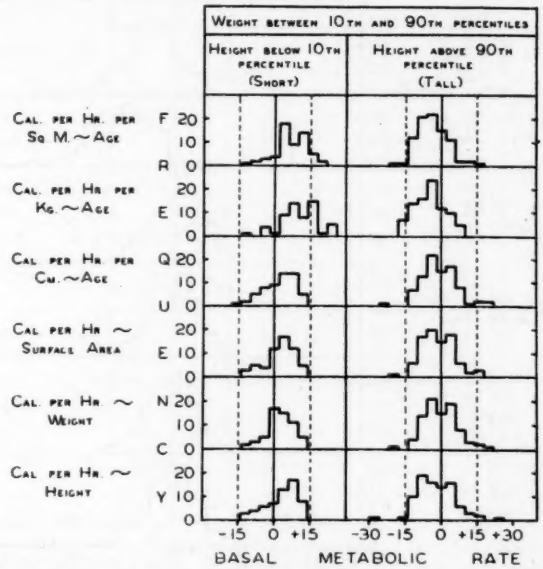
Weight between 10th and 90th percentiles
Height below 10th percentile (Short)
Height above 90th percentile (Tall)
Cal. per Hr. per Sq M.~Age
Cal. per Hr. per Kg.~Age
Cal. per Hr. per Cm.~Age
Cal. per Hr. ~ Surface Area
Cal. per Hr. ~ Weight
Cal. per Hr. ~ Height
F 20 10 R 0
20 E 10 0
Q 20 10 U 0
20 E 10 0
N 20 10 C 0
20 Y 10 0
-15 0 +15
-30 -15 0 +15 +30
BASAL METABOLIC RATE

Chart 3. Frequency distribution of percentage deviation of basal metabolism, for each of 6 methods of reference indicated on ordinate, of Child Research Council children whose weight falls in median 80% and whose height falls either below 10th percentile or above 90th percentile of values for children on whom Council standards were established. Solid vertical lines represent value of theoretic zero and broken vertical lines range of minus 15 to plus 15%.

for the "thin" children. These are the same three methods of reference found to give the most consistent results for the "small" and "large" children. When cal./hr./kg. referred to age is the method of reference used, 29% of the values fall above plus 15% for the "thin" children and 30% of the values fall below minus 15% for the "obese" children. The reverse is true for cal./hr./cm. referred to age and for cal./hr. referred to height, although not more than 19% of the values fall outside of the range of plus or minus 15%. It is interesting to note that these displacements for the respective methods of reference are in one direction for the "small" and the "thin" children and in the opposite direction for the "large" and the "obese" children (cf. charts 1 and 2).

The BMR for the "short" and the "tall" Council children are given in chart 3. The majority of BMR for 58 tests on the "short" children fall on the positive side for all

six methods of reference, yet between 88 and 100% of the values stay within the range of minus 15 to plus 15%, with the single exception of cal./hr./kg. referred to age, which shows a marked shift to the right. In this instance 36% of the tests are higher than plus 15%. The BMR for the 89 tests on the "tall" children, on the other hand, show a moderately even distribution within the range of minus 15 to plus 15% for all six methods of reference, although there is a slight tendency for more of the values to fall on the negative than on the positive side. Thus, for the "short" and the "tall" children, there appears to be little preference as to the methods of reference to be used.

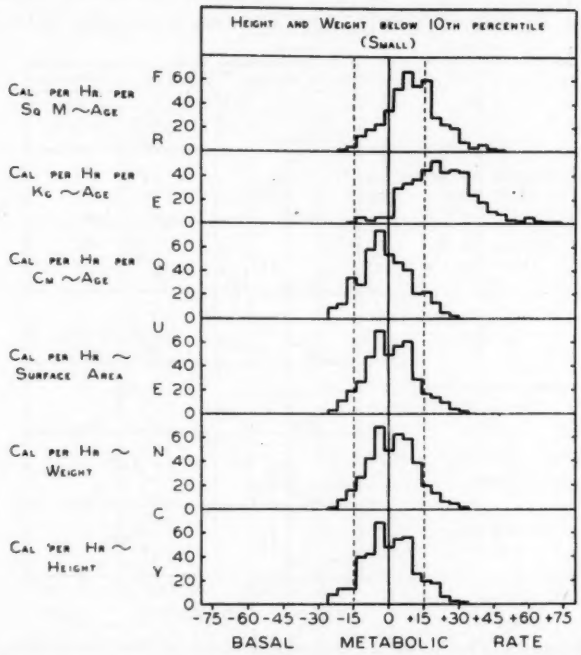
HEIGHT AND WEIGHT BELOW 10TH PERCENTILE
(SMALL)
CAL PER HR. PER SQ M ~AGE
CAL PER HR PER KG ~AGE
CAL PER HR PER CM ~AGE
CAL PER HR ~ SURFACE AREA
CAL PER HR ~ WEIGHT
CAL PER HR ~ HEIGHT
FREQUENCY
0 20 40 60
-75 -60 -45 -30 -15 0 +15 +30 +45 +60 +75
BASAL METABOLIC RATE

CHART 4. Frequency distribution of percentage deviation of basal metabolism, for each of 6 methods of reference indicated on ordinate, of children reported in literature whose height and weight fall below 10th percentile of values for children on whom Child Research Council standards were established. Solid vertical line represents value of theoretic zero and broken vertical lines range of minus 15 to plus 15%.

From these results on Child Research Council children it may be seen that for all six types of body build the method of reference of cal./hr./sq. m. referred to age gives values which fall consistently within the range of minus 15 to plus 15%, although for "short" children there is a tendency for results to fall on the positive side. When calculated on the basis of cal./hr. referred to surface area and of cal./hr. referred to weight, the values fall, in most cases, within this same range. As for cal./hr./kg., cal./hr./cm., each referred to age, and cal./hr. referred to height, the BMR fall to a much greater degree outside of the minus 15 to plus 15% range.

In the analysis of the data from the literature, the Child Research Council standards[2] were likewise used. Chart 4 shows the percentage deviation of the basal metabolism

reported in the literature[3-37] for 421 tests on "small" children. Of the six methods of reference, the values obtained for cal./hr./cm. referred to age and cal./hr. referred to surface area, weight and height, respectively, show a good distribution within the range of minus 15 to plus 15%. Thirty-six per cent of the values for cal./hr./sq. m. referred to age, and 72% of those for cal./hr./kg. referred to age fall above plus 15%. When these results are compared with those found on the Child Research Council children (chart 1), it may be seen that all BMR shown in chart 4, regardless of the method of reference, are shifted to a greater degree toward the positive side. This discrepancy is probably

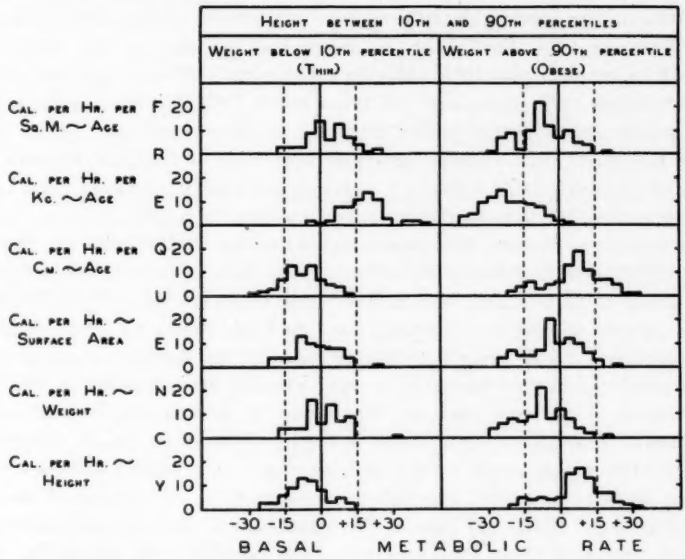

CHART 5. Frequency distribution of percentage deviation of basal metabolism, for each of 6 methods of reference indicated on ordinate, of children reported in literature whose height falls in median 80% and whose weight falls either below 10th percentile or above 90th percentile of values for children on whom Child Research Council standards were established. Solid vertical lines represent value of theoretic zero and broken vertical lines range of minus 15 to plus 15%.

explained by the fact that many of these children are definitely smaller than the Council children who fall in the lower 10% for height and weight. A positive deflection for cal./hr./sq. m. referred to age was also found by Iliff, Gordon, McNamara and Bell[38] on a small number of nonhypothyroid dwarfs. When calculated on the basis of the Council standards for cal./hr./sq. m. referred to age, BMR were found by these authors to vary between plus 3 and plus 44%, but only 2 of the 9 determinations on these 6 dwarfs fell below plus 15%. Thus, for children who are extremely small, high BMR may be expected with the method of reference of cal./hr./sq. m. referred to age; while for the Council children who are of less extreme build, this marked positive bias does not exist. However, when cal./hr. referred to surface area, to weight, or to height, respectively, are the standards used, the data, both on "small" Child Research Council children and on "small" children reported in the literature, give at least 80% of the values within the range of minus 15 to plus 15%.

In the literature,[4, 7, 8, 11, 31, 39–42] the number of "large" children is insufficient to show graphically, but the BMR for each of the six methods of reference fall into a distribution which does not differ significantly from that found for the "large" Council children (chart 1). Likewise, the values found on the few "tall" children[4, 7, 8, 11, 16, 19, 25, 41, 43] show a pattern similar to that of the "tall" children of the Child Research Council (chart 3).

Chart 5 depicts the BMR for the six methods of reference of "thin" and "obese" children, respectively, reported in the literature. For cal./hr./sq. m. referred to age and for cal./hr. referred to surface area and weight, respectively, 85% or more of the BMR found on the 65 "thin" children[4, 8, 10–12, 14, 15, 17, 27, 29–31, 33–37] and 71% or more of the 90 tests on the "obese" children[3, 4, 6–8, 11, 13, 18, 24, 31, 37, 39–44] fall within the range of minus 15 to plus 15%. For cal./hr./kg. referred to age, 68% of the "thin" children have BMR higher than plus 15% while for cal./hr./cm. referred to age and for cal./hr. referred to height 20% of the tests fall below minus 15%. For these methods of reference, opposite and somewhat greater variations are found with the "obese" children. All these histograms show a similar pattern to those based on the Child Research Council children of like body build (chart 2), although more BMR of these "obese" children fall below minus 15% than do the values for the Council children.

In an attempt to evaluate this greater number of low BMR found for the "obese" children reported in the literature as compared with those of the Council, the values for another group of children were also studied. These data were obtained by Gordon*[38] on his obese patients at New York Hospital. Since the Child Research Council standards[2] do not as yet extend above 44 kg. for girls or above 50 kg. for boys, many of the New York Hospital children are too large to make possible the calculation of the BMR by all six methods of reference. However, 80 tests on 74 children who do come within the Child Research Council range are shown in chart 6. Calories/hr./sq. m. referred to age and cal./hr. referred to weight are the methods of reference which show the least deviation from the average values, although from 14 to 16% fall outside of the plus or minus 15% range. Thirty per cent of the values for cal./hr. referred to surface area are higher than plus 15%. Basal metabolic rates calculated for cal./hr./kg. and for cal./hr./cm., each referred to age, and for cal./hr. referred to height show displacements in the same direction as those represented in charts 2 and 5 for the two other series of children who have this type of body build. However, the deviations are greater here than with the Council children, although there are not as many negative values as are found on the "obese" children reported in the literature. At the present time no explanation for this discrepancy is evident.

The 322 determinations of basal metabolism reported in the literature[3–8, 10–13, 15–31, 33–37, 39–42, 44–47] for "short" children are presented in chart 7. These BMR for the methods of reference of cal./hr. referred to surface area and cal./hr. referred to weight give a fairly even distribution, although about 15% of the tests fall outside of the range of minus 15 to plus 15%, while those for the other methods of reference show a tendency to fall on the positive side. This tendency toward positive BMR is more marked for these children than for "short" children of the Council (chart 3), since from 15 to 30% of the tests have a basal metabolic rate above plus 15%. The some-

* The authors wish to express their appreciation to Dr. Harry H. Gordon for the use of his unpublished data.

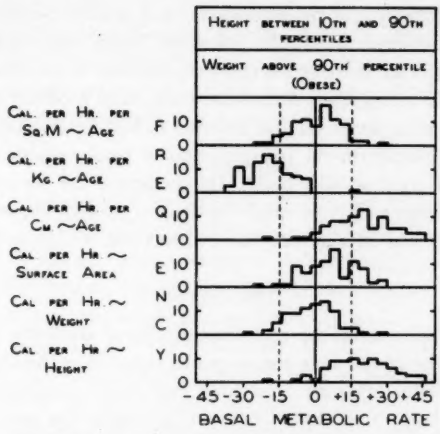
Height between 10th and 90th percentiles
Weight above 90th percentile (Obese)
Cal. per Hr. per Sq. M ~ Age
Cal. per Hr. per Kg. ~ Age
Cal. per Hr. per Cm. ~ Age
Cal. per Hr. ~ Surface Area
Cal. per Hr. ~ Weight
Cal. per Hr. ~ Height
F R E Q U E N C Y
10
0
-45 -30 -15 0 +15 +30 +45
Basal Metabolic Rate

CHART 6. Frequency distribution of percentage deviation of basal metabolism for each of 6 methods of reference indicated on ordinate, of New York Hospital children whose height is in median 80% and whose weight is above 90th percentile of values for children on whom Child Research Council standards were established. Solid vertical line represents value of theoretic zero and broken vertical lines range of minus 15 to plus 15%.

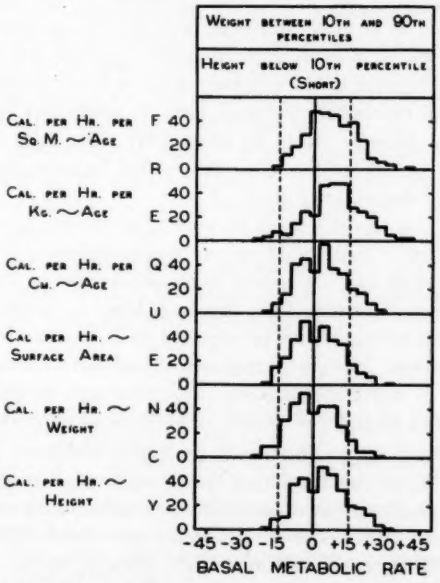
Weight between 10th and 90th percentiles
Height below 10th percentile (Short)
Cal. per Hr. per Sq. M. ~ Age
Cal. per Hr. per Kg. ~ Age
Cal. per Hr. per Cm. ~ Age
Cal. per Hr. ~ Surface Area
Cal. per Hr. ~ Weight
Cal. per Hr. ~ Height
F R E Q U E N C Y
40
20
0
-45 -30 -15 0 +15 +30 +45
Basal Metabolic Rate

CHART 7. Frequency distribution of percentage deviation of basal metabolism, for each of 6 methods of reference indicated on ordinate, of children reported in literature whose weight falls in median 80% and whose height falls below 10th percentile of values for children on whom Child Research Council standards were established. Solid vertical line represents value of theoretic zero and broken lines range of minus 15 to plus 15%.

what higher rates probably can be explained, in a manner similar to that previously mentioned in connection with the results found on "small" children, by the fact that the Council children are not as short as the children reported in the literature.

The results obtained on children of unusual body build reported in the literature show that the methods of reference of cal./hr. referred to surface area and cal./hr. referred to weight are the most reliable for the interpretation of basal metabolic rate determinations for children of all six types of body build. The method of cal./hr./sq. m. referred to age is also dependable except with very small children or dwarfs. Reliance cannot be placed upon cal./hr./kg. referred to age, cal./hr./cm. referred to age and cal./hr. referred to height.

Discussion

The validity of basal metabolism tests on children of abnormal body dimensions has been questioned because of the inconsistent results reported in the literature. For example, both Bruch[40] and Wolman[48] have concluded that basal metabolism measurements on children of atypical body build have little clinical value. On the contrary, it has been found in the studies of the Child Research Council that a careful choice of the method of reference gives reliable BMR. In this study it has been demonstrated that, if the proper methods of reference based on reliable standards are employed, the BMR of children with unusual body build are trustworthy and can be of clinical significance. The reliability of the standards from various laboratories has been discussed elsewhere.[2,49] A careful consideration of the discrepancies reported in the literature for the basal metabolism of children of atypical body build warrants the conclusion that the failure of agreement between different workers as to the reliability of the different methods of reference is due to the differences in the standards used in their calculation.

Obviously, the basal metabolism test itself must be satisfactory from the standpoint of technic if the results obtained are to be trustworthy. Care must be taken to have the patient fasting and rested as well as quiet and relaxed in order that the resulting BMR may be valid and so capable of interpretation.

The relationships found in this study between these various methods of reference for BMR and the six types of body build are not surprising. Since height and weight and surface area increase with age, a standard based on any one of these alone actually includes age, even though indirectly. Thus, standards based on height or weight or surface area without reference to age would be expected to be reliable for children who have ordinary body dimensions. However, since weight and surface area give a better indication of the amount of active metabolizing tissue than does height, standards based on weight and surface area should give results for children of unusual body build which can be more readily interpreted than those based on height. Moreover, when the standards of cal./hr./kg. or cal./hr./cm., each referred to age, are used, it is to be anticipated that a child who is out of proportion in either weight or height for his age will give BMR that are very different from those obtained on a well-proportioned child. On the other hand, since height and weight are included in the calculation of surface area, the BMR based on cal./hr./sq. m. referred to age should give values for all children without endocrine dysfunction that are within or close to the range of plus or minus 15%. Thus, it is not surprising that the standards for cal./hr. referred to weight and to surface area, respectively, and for cal./hr./sq. m. referred to age give the most consistent results regardless of body dimensions. It should not be forgotten, however, that the use of the other stand-

ards in conjunction with these three may give valuable information about a child of unusual body build.

It should be emphasized that the basic problem in both diagnosis and treatment is the adequate understanding of the patient as an individual. Indeed, reliable standards of basal metabolism are useful only to the extent that they make possible the proper evaluation of the functioning of individuals of diverse body builds.

Conclusions

The relative predictive value of six methods of reference frequently used to determine the BMR of children of unusual body build has been studied. The methods of reference based on the Child Research Council standards[2] which were employed for this purpose were those for cal./hr./sq. m., cal./hr./kg. and cal./hr./cm., each referred to age, and cal./hr. referred to surface area, weight and height, respectively.

An analysis was made of 558 determinations of basal metabolism obtained on 86 healthy children of the Child Research Council, of 946 basal metabolism tests on 793 children described in the literature and of 80 basal metabolism tests on 74 children observed by Gordon. The study included children between 2 and 16 years of age whose weight or height or both weight and height fell above the 90th percentile or below the 10th percentile of all the children of similar age on whom the Council standards had been established.

The results of this analysis show that the methods of reference of cal./hr. referred to surface area and of cal./hr. referred to weight are reliable for the interpretation of BMR determinations on children of all six types of body build. This is also true of cal./hr./sq. m. referred to age except in the case of very small children or dwarfs for whom high BMR are found. These observations might well have been anticipated since height and weight and surface area increase with age in children, but weight and surface area give a better evaluation of body mass than does height.

The methods of reference of cal./hr./kg. referred to age, cal./hr./cm. referred to age and cal./hr. referred to height are not so reliable, either individually or collectively, for routine clinical use as are the other three methods of reference. Nevertheless, the deviations in the BMR obtained by these less satisfactory methods of reference may be of considerable importance in understanding the problems of a child of unusual body build.

The use of the proper methods of reference based on reliable standards will result in trustworthy BMR for children of unusual body build.

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SPANISH ABSTRACT

La Interpretación del Metabolismo Basal en Niños con Desarrollo Atípico del Cuerpo

Con el objeto de estudiar el valor relativo de exactitud de séis métodos de referencia frecuentemente usados para la determinación del metabolismo basal de niños con desarrollo atípico del cuerpo, se hizo un analisis de 1584 pruebas de metabolismo realizadas en 953 niños saludables, los cuales procedian de estudios hechos por el Child Research Council y también de estudios descritos en la literatura. La edad de los niños osciló entre 2 y 16 años, y en los cuales la talla, ó el peso, ó ambos factores, estaban por arriba del décimo-noveno percentile ó por debajo del décimo percentile en relación a los de niños de edades similares y en los cuales los "standards" del Council fueron establecidos.

Los resultados de este analisis demostró que los métodos de referencia basados en calorias por hora en relación al area de superficie y el de calorias por hora en relación al peso, son los mas exactos para la interpretación de las determinaciones del metabolismo basal de estos niños con desarrollo atípico del cuerpo. Esto también fué cierto para el método basado en calorias por hora por metro cuadrado en relación a la edad a excepción de los casos de niños pequeños o en los enanos, en los cuales se obtiene un metabolismo basal elevado. No existe exactitud alguna en los resultados con los métodos basados en calorias por hora por kilogramo en relación a la edad, ó calorias por hora por centimetro en relación a la edad, ó en calorias por hora en relación a la talla, tanto desde un punto de vista individual ó bien colectivo. Sin embargo, se estima que las desviaciones de metabolismo basal obtenidas con estos metodos de referencia menos exactos pueden tener una importancia considerable en la interpretación de este problema de niños con desarrollo atípico del cuerpo.

En conclusión, se señala que el uso de métodos de referencia adecuados basados en "standards" aceptables resultará en la obtención de un metabolismo basal correcto en niños con desarrollo atípico del cuerpo.

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ATRESIA OF THE INTRAHEPATIC BILE DUCTS

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ATRESIA of the intrahepatic biliary system has received little attention in the medical literature, although more than 250 case reports of infants with various atresias of the extrahepatic bile ducts have been recorded. In the present report four patients are discussed in whom microscopic study failed to demonstrate recognizable biliary epithelium in all portal spaces sectioned. In addition, the clinical histories are remarkable for duration of life exceeding three years in all the patients, and for the unusual physical finding of generalized xanthomatosis of the skin.

Thomson[1] in 1891 first surveyed the medical literature on congenital obliteration of the bile ducts and collected 50 cases. Subsequent reviews were published by Beneke[2] in 1903 (74 cases); Flebbe[3] in 1907 (71 cases); Holmes[4] in 1916 (114 cases); Stolkind[5] in 1939 (276 cases); and by Dahl-Iversen and Gormsen[6] in 1944 (264 cases). Analysis of this large experience demonstrates that the extent of atresia may vary from a small area of partial stenosis in a single duct to complete absence of all extrahepatic biliary structures. It is therefore surprising that so few cases have been recorded in which partial or complete absence of intrahepatic interlobular bile ducts has been observed. Heschl[7] in 1865 reported the first case in which microscopic study showed a complete absence of large and small ducts within the liver. His patient, an infant who died at 7 months of age, also had no trace of hepatic or common ducts. Subsequently 10 cases have been described in which absence or paucity of intrahepatic bile ducts has received special comment (table 1). In three of these cases the extrahepatic bile ducts were found to be normal.

The occurrence of xanthomatosis of the skin in adult patients with primary biliary cirrhosis has been discussed in previous reports.[8–13] Certain of these studies[10–13] have shown that elevation of serum lipids frequently accompanies other signs of biliary obstruction, particularly in the earlier stages of disease prior to the development of liver decompensation. Moreover, the formation of xanthomata in the skin occurs only when the serum lipid elevation is severe and prolonged. In congenital atresia of the bile ducts the development of secondary biliary cirrhosis and hepatic insufficiency is fairly rapid, causing severe malnutrition and death usually before the age of 1½ years.[5] In these circumstances xanthomatosis is not to be expected. Its occurrence in the four patients of the present report, whose nutritional state was good and whose life span was extraordinarily long, fortifies arguments previously presented:[13] that elevation of serum lipids implies functional adequacy of the liver, and that this elevation must be prolonged before xanthomatosis appears.

The present report includes a detailed clinical and pathologic description of two original cases and, in addition, a discussion of microscopic findings in two similar cases,

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(Received for publication Oct. 22, 1950.)

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TABLE 1

Reported Cases of Atresia of Intrahepatic Bile Ducts

No.	Author and Date	Patient's Sex	Age at Onset of Jaundice	Age at Death	Skin Xanthomatosis	Extrahepatic Biliary Tract	Intrahepatic Bile Ducts
1	Heschl,[7] 1865	F	Birth	7 mo.	No	Cystic and hepatic ducts solid cords. Common duct absent. Gallbladder rudimentary.	No large or small ducts.
2	Feer,[44] 1903	M	3 days	10 mo.	No	Absence of entire tract.	Absence of large ducts. Small ducts duplicated, in part compressed, in part dilated. Numerous bile plugs.
3	Paul,[45] 1922	?	3 days	5½ mo.	No	Absence of entire tract.	Absence of large ducts.
4	Vigholt,[46] 1928	M	Birth	3 mo.	No	Absence of entire tract.	Absence of large ducts. Few small ducts, no lumens. Plugs in canaliculi.
5	Sweet,[47] 1932 siblings Case 1	F	Birth	1 yr.	No	Hepatic ducts solid cords. Gallbladder, cystic and common ducts very small.	Large ducts scarce and shrunken. No small ducts and no proliferation. Plugs in canaliculi.*
6	siblings Case 2	M	3 days	7 wk.	No	Common and hepatic ducts solid cords. Gallbladder distended, cystic duct narrow.	Large ducts decreased in number and shrunken. Few small ducts, no proliferation. Plugs in canaliculi.*
7	Finlayson,[14] 1937	F	<7 days	3½ yr.	Yes, at 1½ yr.	Hepatic and common ducts solid cords. Gallbladder and cystic duct patent.	No large or small ducts. Plugs in canaliculi.*
8	Dahl-Iversen and Gormsen,[5] 1944 Case 1	F	Birth	7 mo.	No	Absence of entire tract.	Absence of large ducts. Proliferation of smallest ducts with bile plugs.
9	Case 2	F	Birth	Died at birth	No	Normal	No ducts in 42 out of 50 portal spaces. Ducts normal in 8 of 50 spaces, no duplication. No bile plugs.
10	Sacrez et al.,[48] 1946	F	8 days	3½ yr.	No	Normal	Scarcity of large and small ducts, none in 90 of 100 portal spaces.
11	Dobbs,[13] 1949	F	2 days	3 yr.	Yes, at 1½ yr.	Normal	No large or small ducts. Plugs in canaliculi.*
12	Ahrens, et al. 1950 Case 1	F	Birth	3½ yr.	Yes, at 1½ yr.	Gallbladder 6×1 cm., distended. Cystic duct patent, common duct patent but 1 mm. in diam. Rt. hepatic duct patent, 1 mm. No left hepatic duct found.	No large or small ducts. Plugs in canaliculi*
13	Case 2	M	2 days	Living at 5 yr.	Yes, at 3½ yr.	Normal gallbladder, bulbous cystic duct ending in narrow duct. Common duct narrow but patent. Hepatic ducts solid cords. Verified by cholangiogram.	No large or small ducts. Plugs in canaliculi.*

* Sections reviewed by present authors.

TABLE 2

LABORATORY INDICES OF BILIARY OBSTRUCTION*

	Serum Bilirubin		Alkaline Phosphatase Bodansky u./100 cc.	Serum Lipids, mg./100 cc.						Phenol Turbidity u./100 cc.
						Cholesterol			"Neutral Fat"	
	Direct mg./100 cc.	Total mg./100 cc.		Total Lipids	Phospho-lipids	Total	Free	Free / Total		
Case 1										
Dec. 1945	8.3	16.7	71			449				
Jan. 1946			47							
May 1946	7.6	15.0	76							
Oct. 1946						1816	1566	0.86		
Jan. 1948	5.3	11.7		1965	930	550	471	0.86	432	59†
Mar. 1948				867	330	200	140	0.70	297	19†
Apr. 1948	9.2	22.7	9	610	270	149	83	0.56	147	24†
May 1948			15	2092	956	566	446	0.79	490	63†
May 1948				2138	1088	633	507	0.80	338	67†
July 1948				1220	675	400	328	0.82	97	31†
Case 2										
Dec. 1948	4.1	9.1	31	3449	1713	1020	730	0.72	521	54‡
Jan. 1949	4.0	10.3	31	2592	1250					33‡
Jan. 1949	5.0	9.0	22	2487	931	812	534	0.66	558	34‡
Feb. 1949	4.7	7.9	26	1847	775	687	424	0.61	209	27‡
Oct 1949	2.2	5.8	50			970	640	0.66		24‡
May 1950	2.0	5.4	28							27†

* For methods, see reference 13.
† 1:30 dilution of serum with phenol reagent.
‡ 1:100 dilution of serum with phenol reagent.

TABLE 3

TESTS OF HEPATIC FUNCTION*

	Serum Albumin	Serum Globulin	Serum Fibrino-gen	Pro-thrombin Time	Serum Esterase Activity	Cephalin Floccula-tion	Thymol Turbidity	Zinc Turbidity	Brom-sulfalein Retention
	gm./100 cc.		mg./100 cc.	sec.	u./100 cc.		u./100 cc.		% at 45 min.
Case 1.									
Dec. 1945	5.3	2.2				0			
Jan. 1946				15					
Jan. 1948	3.9	3.5	390		56			15	
Mar. 1948								18	
Apr. 1948				16.6	37	0	3	21	
May 1948	3.9	4.3	540		54		7	24	
June 1948				13.5					
Case 2.									
Dec. 1948	3.8	2.9	330	16.6		+	3+	7	19
Jan. 1949				15.3		0	2+	3	39
Feb. 1949	4.3	2.9						4.4	
Oct. 1949	4.0	2.8				0	0	3.4	
May 1950								16	

* For methods, see reference 13.

the clinical histories of which have already been published by Finlayson[14] and by Dobbs.[15] Brief descriptions of the present authors' two original cases have been presented separately[13] as part of a detailed study of primary biliary cirrhosis.

Case Reports

Case 1. E. McH., a Negro girl, the 5th child of healthy parents, was born at 8 mo.' term weighing 2.4 kg. Jaundice was noted in the 1st wk. of life and persisted until death at 3½ yr. of age. Stools were continuously clay-colored and of putty-like consistency; urine was deep orange in color. She developed slowly, was able to sit at 1½ yr. and stood at 3 yr., but could not walk alone. She did not talk but appeared to understand conversation.

When seen for the 1st time at 1 yr. of age, icterus was plainly visible in sclerae and on palms and soles. The anterior fontanelle was wide. Prominent bilateral epicanthic folds were present. Lower jaw contained 2 green incisors. Liver extended 4 cm. below R costal border and was firm. Spleen was not felt. Some lymph nodes were enlarged. Clinical and roentgenographic evidence of atrophic rickets was definite. Studies of blood (tables 2 and 3) were consistent with extreme biliary obstruction, but showed good albumin synthesis and a negative cephalin flocculation. Blood was Wassermann-negative, Group O, Rh-positive; no sickling. Three attempts at duodenal drainage carried out under fluoroscopic observation yielded thick colorless fluid, acid in reaction. Urine showed a positive test for both bilirubin and urobilin. Quantative urobilinogen measurements were not made. Stool fats were 2.99 gm./day, serum Ca 7.6 mg./100 cc. and P 2.6 mg./100 cc.

Healing rickets was demonstrated roentgenographically 3 wk. after intramuscular injection of 600,000 I. U. of irradiated 7-dehydrocholesterol (vitamin D_3) and was accompanied by a significant decrease in serum alkaline phosphatase activity. Rickets was thereafter controlled by oral vitamin D. Serum calcium and phosphorus levels returned to normal. Nevertheless, severe osteoporosis with dilation of medullary cavities was found at all future examinations.

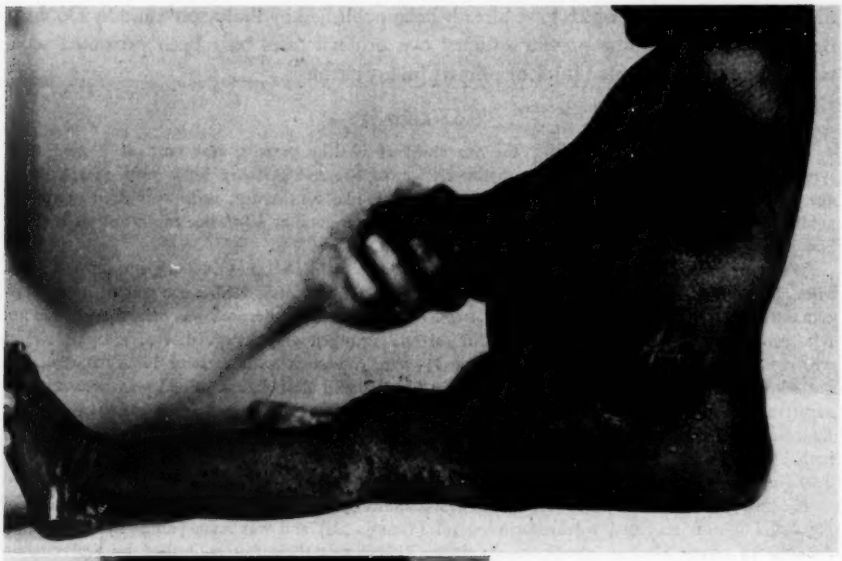
Exploratory laparotomy at 13 mo. of age revealed no evidence of gall bladder and no bile ducts. Liver was firm, green-brown and smooth. Reconstructive surgery was not attempted. A small piece of liver removed by biopsy showed absence of bile ducts of all sizes. There were many bile plugs in bile capillaries. Slight increase in fibrous tissue and mild mononuclear infiltration in portal areas was seen. Hepatic cord cells were normal, except for presence of granules of bile pigments.

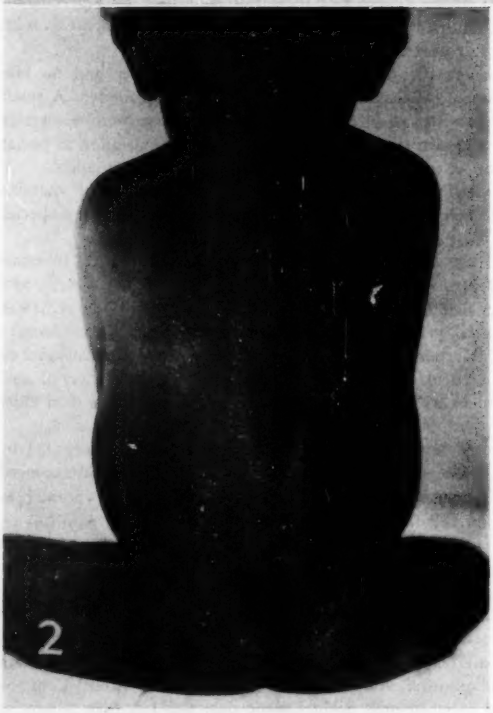
Postoperatively, a low-fat, low-starch, high-protein diet was given with supplements of vitamins A, B, C and D and pancreatin. As she ate poorly, except for milk, attempts at maintaining a special diet were discontinued 1 yr. later.

Pruritus was first noted at 1½ yr. of age and jaundice remained intense. At 1¾ yr. tuberous xanthomatous lesions appeared on finger tips, knees, ears and around the rim of the nostrils and they gradually became more extensive so that at 3 yr. almost the entire surface of the skin was involved (Figs. 1 and 2). Lesions were raised, yellow and smooth, and originally discrete xanthomata tended in some areas to become confluent. Mucous membrane lesions were not seen. The remainder of the skin was dry, coarse and thickened, particularly over the lower legs and feet. At 3 yr. of age, many xanthomata began to resolve, coincident with a fall in total serum lipids from more than 2000 mg./100 cc. to about 900 mg./100 cc.

Frequent bleeding from the nose became troublesome at 1½ yr. of age but was controlled by daily doses of oral vitamin K. Bleeding from gums became severe after 3 yr. of age and appeared to originate around carious, broken green teeth. Although prothrombin times were normal as long as vitamin K supplements were given, blood loss was large and Hgb. fell to 2 gm./100 cc. Coma was followed by death at 3½ yr. of age. At the last hospital admission, liver edge was felt 8 cm. below costal border and spleen 4 cm.

Postmortem examination showed pallor, jaundice, extensive xanthomatosis of skin and palpable lymph nodes in inguinal, axillary and cervical regions. There was frontal bossing, beading of ribs and a Harrison's groove. There was no ascites. Liver weighed 800 gm., was green, normal in shape, slightly granular on surface and firm. Gall bladder measured 5 x 1 cm., was distended with dark green viscid material and was in normal position. Ampulla of Vater was stained green. Common duct was 1 mm. in diameter, patent and green-stained. Right hepatic duct was less than 1 mm. in diameter, patent and bile-stained. Left hepatic duct consisted entirely of fibrous tissue, and no lumen could be identified under a dissecting microscope. This fibrous strand was not bile-stained.





FIGS. 1 and 2. Case 1 (Negro) at 3 yr. Xanthomatosis of tuberous type involving arms, legs and trunk. Note coarseness and thickening of skin over ankles and knees. See also Fig. 12 in reference 13.

Bile ducts were not seen grossly on sectioning liver. Other congenital anomalies were not noted. Spleen weighed 45 gm.; pancreas was normal. Very small yellowish plaques of less than 1 mm. diameter were found in the intima of pulmonary artery, on the aortic leaf of mitral valve and in the endocardium below the aortic ring. Aortic intima was yellow but clean and smooth. There was no kernicterus.

Microscopic examination of 5 different blocks of hepatic tissue taken from both main lobes failed to show a single recognizable bile duct, either of the large columnar-cell type with wide lumen or of the low cuboidal-cell type (cholangiole) lying near the hepatic cords. Fibrous tissue was moderately increased, both in and around lobules, and lobular disorganization was marked in some areas. There was slight diffuse mononuclear infiltration in some portal areas, and occasional polymorphonuclear leukocytes were found within the lobules. Hepatic cells were markedly bile-stained and

FIGS. 3 and 4. Case 2 at 3¾ yr., showing good nutritional state, enlargement of liver and spleen, and small tuberous xanthomata of knees and finger tips.

bile plugs in canaliculi were common. Foam cells were not seen and stains for iron and fat were negative. Sections of skin showed accumulation of foam cells typical of xanthomatous infiltration.[8]

Case 2. P. R., a boy, 6th child of healthy parents, was born at full term, weighing 2.8 kg. One sibling died at 6 days of age of intestinal atresia; the other 4 were living and well. Jaundice was noted on the 2nd day of life; stools were pale and urine was deep orange. These signs of biliary obstruction have been present with varied intensity at all times during this patient's 5 yr. Jaundice has been most severe during episodes of respiratory tract infection. Enlargement of liver and spleen was first noted at 7 wk. of age and has been present at all subsequent examinations. Pruritus became distressing in the 3rd yr. of life and at 3½ yr. tuberous xanthomata appeared for the first time on fingers, toes and knees. Parents refused surgical intervention. Supportive care included a low-fat diet and daily supplements of fat-soluble vitamins, vitamin B, folic acid, choline and inositol. At 3¾ yr. of age, when patient was seen for the first time, jaundice and pruritus were moderately severe and xanthomata were numerous (Figs. 3 and 4). There were dilated veins on the abdominal wall but no ascites. Liver edge was felt 5 cm. below R costal border, spleen 6 cm. below costal margin. There was no clubbing of fingers or toes. Deep reflexes were absent in knees and ankles, and positive Babinski, Chaddock and Oppenheim reflexes were elicited. There were no Kaiser-Fleischer rings and no dystonia.

Laboratory studies (tables 2 and 3) showed high grade biliary obstruction, moderate normochromic anemia and increased erythrocyte resistance to hypotonic sodium chloride solutions. Patient's blood was Wassermann-negative, Group B, Rh-positive; mother was Group O, Rh-positive. Stools con-

tained 7.2 gm. fat/day on a normal diet, more than 3 times normal quantity. RGs showed rarefaction of all long bones but no signs of rickets. Cholecystograms failed to show a gall bladder shadow.

Exploratory laparotomy was performed at 4 yr. of age. There was no ascites. Liver was large, green, finely granular and normal in contour. Gall bladder measured 2.5 x 0.5 cm. and contained a small amount of dark green bile. A bulbous cystic duct ended in a narrow, cord-like common duct which was traced caudally to the duodenum, and cephalad to hepatic ducts which appeared to be completely stenosed. Diodrast (5 cc. of 35% solution) was injected under pressure into gall bladder. Cholangiograms showed a very thin stream of diodrast between gall bladder and duodenum with pooling in duodenum, but there was no penetration of contrast medium into either hepatic duct. A cholecystojejunostomy and Roux-type jejunojejunostomy were performed, although combined surgical and radiologic findings were interpreted to indicate marked stenosis or atresia of hepatic ducts with partial stenosis of common duct.

Postoperatively jaundice increased and liver and spleen enlarged, but these changes were only temporary. At 4½ yr. of age, fecal urobilinogen content was 17 mg./day. At present, at 5½ yr. of age, patient is still active but remains jaundiced and itching. Recently there have been numerous episodes of frequent bowel movements. There has been no significant change in xanthomata. He has had no hematemeses or bleeding tendency. Liver and spleen are 4 and 6 cm. below rib margins, respectively.

Microscopic study of the biopsy material taken from the liver during laparotomy showed 7 definite portal spaces and 15 lobules. In none of these spaces were recognizable large or small bile ducts to be found. There was marked retention of bile pigments in hepatic cells and distention of canaliculi with bile plugs. A few mononuclear and rare polymorphonuclear cells were found in the portal spaces and occasional polymorphonuclears were seen within the lobules. Lobular architecture was somewhat disorganized and there was a slight increase in fibrous tissue in portal areas. Foam cells were not seen and sections stained for fat and iron showed no abnormalities.

Case 3. H. L., a girl, the 1st child of a healthy mother, was previously reported in detail by Finlayson.[14] Jaundice occurred in the 1st wk. of life and remained severe until death at 3¼ yr. of age. At the same time, stools became clay-colored and urine dark, remaining so until death. Liver edge was felt 1 cm. below costal border at 10 mo. of age. At this time, clinical and roentgenographic rickets were definite. Blood Wassermann test was negative. Laparotomy at 11 mo. of age showed gall bladder to be small, white, empty and thick-walled, and all ducts were white and cord-like. Reconstructive surgery was not attempted. A fish liver oil concentrate was given in large doses with marked improvement in rickets. Pruritus was noted at 13 mo. of age and became severe. Generalized xanthomata of skin appeared at 15 mo. and were exuberant until 29 mo. of age, when they began to resolve. At 39 mo., jaundice was intense, but pruritus had disappeared; xanthomata had almost vanished; liver was enlarged to level of umbilicus and spleen filled the entire left abdomen; teeth were carious and broken. There was a hypochromic anemia with Hgb. 7.3 gm./100 cc. She died at 40 mo. of age following an episode of pharyngitis with fever, complicated by appearance of subcutaneous hemorrhages and bleeding from gums.

Postmortem examination showed deep jaundice, very little subcutaneous fat and no ascites. Liver was large, firm, olive-green and smooth. Hilar glands were not enlarged, although mesenteric glands were larger than normal. Gall bladder measured 3 x 1 cm. and contained bile. Cystic duct was bile-stained and patent for 1 cm. and then became a thick fibrous cord which extended to the ampulla of Vater. Hepatic ducts were not identified. Spleen weighed 550 gm.; pancreas was normal. Both kidneys contained multiple abscesses. There were no other congenital anomalies.

Stained sections were furnished to the present authors by Dr. Finlayson. Large bile ducts and cholangioles were completely lacking in all portal spaces. There was considerable distortion of normal lobular architecture by moderately increased amounts of both inter- and intralobular fibrous tissue. Many canaliculi were distended with bile, and in some areas hepatic cells contained granules of bile pigment. Mononuclear infiltration in portal areas was slight, and polymorphonuclear cells were not seen. No foam cells were seen in lobules or portal areas. A section of xanthomatous skin showed foam cells.

Case 4. Dobbs,[15] briefly reporting the case of E. H., a girl, has furnished the following complete clinical report to the present writers: Patient was born at full term, weighing 2.9 kg. She was the 2nd child of healthy parents; mother was toxemic during both pregnancies; sibling, 2 yr. older than patient, was living and well. Jaundice was noted at 2 days of age and persisted with varying intensity

through patient's 3 yr. of life. Stools were constantly clay-colored for 1st 2 mo. and were thereafter yellow and occasionally brown. Urine was not recorded as dark until terminally; there were occasional negative tests for bilirubin in urine at 5 mo. of age, but thereafter all tests were positive. Appetite was always good, but gains in height and weight were slow. She walked alone at 18 mo. and spoke only a few words at the time of death at 3 yr. of age.

Pruritus was noted at 5 mo. of age, at time of 1st hospital admission. She showed moderately severe jaundice and numerous petechial hemorrhages. There was no glandular enlargement. Abdomen was not distended; liver edge was smooth, firm and 3 cm. below costal margin; spleen was just palpable. Laboratory tests included a negative Wassermann reaction, Hgb. 11.3 gm./100 cc., RBC

FIGS. 5 and 6. Case 4 at 2½ yr., showing tuberous xanthomata involving face, hands, knees, soles and ankles. Palms also were affected. Nutritional state was good.

count 3.79 million/cmm., normal leukocyte and differential counts. Child's blood was Rh-negative, mother Rh-positive.

Patient's course was marked by an episode of presumed peritonitis at 16 mo. of age. She responded well to intravenous fluids and sulfonamides. At 20 mo. xanthomatous deposits were noted for the first time, appearing on palms and soles, over elbows, knees and malleoli, around rims of nostrils and along margins of the gums (Figs. 5 and 6). These lesions increased in size and number during remainder of patient's life.

At 2 yr., 5 mo., physical examination showed anterior fontanelle to be wide; teeth were green, carious and loose. Liver was felt 1 cm. below costal margin and was firm, smooth and not tender; spleen was 2 cm. below ribs. Neurologic and funduscopic examinations were normal. Laboratory tests showed Hgb. 10.5 gm./100 cc., RBC count 4.06 million/cmm., normal leukocyte and differential counts, normal erythrocyte fragility. Prothrombin time was 58% of normal, albumin 4.1 gm./100 cc., globulin 2.2 gm. Serum bilirubin was 4.5 mg./100 cc., alkaline phosphatase 36 King-Armstrong units, thymol turbidity 25 units, cephalin flocculation negative. Total serum cholesterol was 1056 mg. and 1081 mg./100 cc. on 2 occasions; free cholesterol 832 mg. (Determinations of serum cholesterol in mother and sister were normal.) Blood urea concentration was 105 mg./100 cc.; urinalyses showed sp. gr. 1.020 and only a few leukocytes. Roentgenograms of skull and long bones were normal, and cholecystograms showed no filling. Two analyses of fecal urobilinogen gave

results of 26.5 mg. and 9.6 mg./day. Skin biopsy showed typical xanthomatous foam cells. A cholesterol-free diet for 1 mo. failed to alter the level of cholesterol in the serum.

At 2¾ yr. of age jaundice became deeper, patient grew listless and anorexic and began to lose weight. Urine became dark but stools remained colored. Serum bilirubin rose to 13.6 mg./100 cc.; alkaline phosphatase increased to 41 King-Armstrong units and thymol turbidity fell to 8 units; Hgb. fell to 7.5 gm./100 cc. Elevated temperature on 2 occasions seemed to respond to penicillin, but the child died at 3 yr. of age in a 3rd episode of fever.

Postmortem examination showed a thin, deeply jaundiced child with generalized xanthomatosis of skin. There was no ascites. Liver was large, green, firm and normal in shape. Gall bladder contained a moderate amount of thin brownish fluid which could be expressed through common duct into the duodenum. Cystic, hepatic and common ducts were patent and normal in size. Spleen was large, pancreas normal. Coronary arteries, myocardium and valves of heart were normal, but a fine whitish deposit was found in the intima of pulmonary artery, in a small area of ascending aorta and in L auricle. There were xanthomatous streaks in the epiglottic folds, but no gross xanthomatous involvement of tendons, liver, gall bladder, bile ducts or spleen was encountered. There was no lymphadenopathy. Brain showed no kernicterus. Kidneys were enlarged and showed heavy inflammatory infiltration in cortex and medulla. Congenital anomalies were not noted. Sections of pulmonary artery showed collections of foam cells in intima, and numerous foam cells also were found scattered throughout splenic pulp. Bone marrow also contained occasional foam cells. Sections of the kidneys showed bilateral acute pyelonephritis.

Two large pieces of liver fixed in formalin were furnished to the present authors by Dr. Dobbs. Sections of these 2 samples of tissue showed complete absence of large and small bile ducts in all portal areas. There was a moderate increase in extralobular fibrous tissue and definite disorganization of lobular architecture. There was a patchy infiltration of portal areas by lymphocytes and an obvious polymorphonuclear leukocytosis throughout the sinusoids. There was irregular bile stasis with inspissated bile casts in canaliculi and some pigmentation of Kupffer cells. Kupffer cells were hypertrophic and hyperplastic and showed retention of foamy material. There were focal collections of these cells in many of the lobules, and these nests were often infiltrated by leukocytes. Sudan IV stains showed small red droplets in the Kupffer cells and in macrophages in a few of the portal areas. Many more fine droplets were visualized in both locations by Sudan black, but even in these sections a large part of foamy cytoplasm of the Kupffer cells remained unstained. Carbol fuchsin stains did not suggest ceroid. Hepatic cells took none of these fat stains. Interpretation of these unusual microscopic findings is rendered difficult by prolonged fixation of tissues in formalin.

Discussion

1. Growth: Growth was significantly retarded in 3 of 4 cases, as shown in chart 1. Slow gains in height and weight are usual in patients with congenital atresia of the extrahepatic bile ducts and are considered to be due to the development of secondary biliary cirrhosis and progressively severe hepatic dysfunction. Defective absorption of fatty foods has been demonstrated in a number of metabolic studies,[16] and loss of calories from this important source would appear also to be a significant contributing factor. The relatively normal development of Patient 2 seems compatible with the minor degree of hepatic fibrosis demonstrated at 4 years of age and with his prolonged span of life.

2. Elevation of Serum Lipids and Development of Xanthomatosis: Previous reports[10–13] have described the elevation of the serum lipids which is characteristic of biliary obstruction. Regardless of the site of obstruction, whether intra- or extrahepatic, the characteristic pattern of the serum lipids consists primarily of an elevation of the phospholipids and, second in magnitude, of free cholesterol. Cholesterol esters and "neutral fat" fractions are normal or slightly elevated. Despite this hyperlipemia the fasting serum is typically clear, and a normal postprandial lipemia is regularly found. The clarity of such high-lipid sera has been the subject of a separate report,[17] in which evidence was presented to substantiate the conclusion that the surface-activity of the phospholipids accounts for

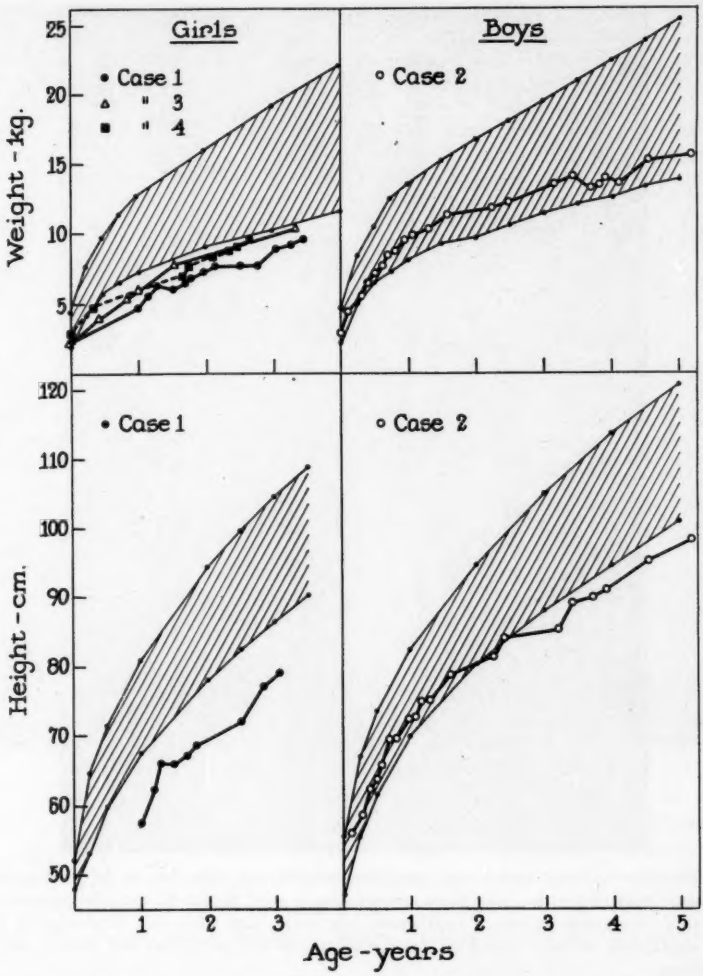


CHART 1. Gains in height and weight of present patients. Shaded areas include normal means ±2½ S.D., smoothed from data of Simmons.[49]

the presence in such sera of lipid droplets too small to be visible. Finally, it has been pointed out that the lipid pattern of biliary obstruction is unlike that found in any other hyperlipemic condition.

In the two original cases of this report the serum lipids were grossly elevated and conformed to the pattern described above (table 2). In Case 3 the serum lipids were apparently not measured, while in Case 4 there was a six-fold elevation of the serum cholesterol level above normal.

In a series of 17 patients with primary biliary cirrhosis,[10] it was found that the development of xanthomatosis of the skin was correlated with the degree of the serum lipid

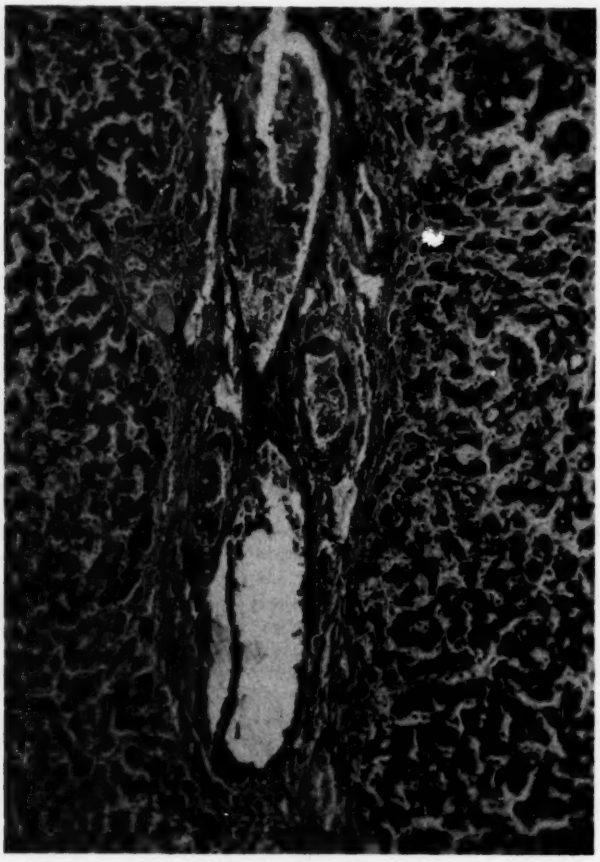


FIG. 7A. Case 1. Large portal area containing arteries and veins but no bile ducts. Increased fibrous tissue with penetration into lobular peripheries is seen. H and E. x 91. B (opposite page). Control case—congenital atresia of extrahepatic bile ducts. Same stain and magnification, showing obvious duplication of small bile ducts (cholangioles), as well as fibrosis and lobular invasion by fibrous tissue.

elevation and with its duration. Thus, those patients who maintained a level of total serum lipids higher than 2000 mg./100 cc. for six months or more gradually developed generalized xanthomatosis. In a lower range (approximately 1300-1800 mg./100 cc.) xanthomata restricted to the eyelids (xanthelasma) occurred, while those patients whose serum lipids never rose above 1300 mg./100 cc. were not observed to develop xanthomatosis of any type. When in the normal course of the disease the serum lipids fell below 1800 mg./100 cc., the decrease was regularly accompanied by resolution of skin xanthomata, even in the most florid cases.

In the present cases, xanthomatosis of the skin appeared at 1¾, 3½, 1½ and 1⅔ years of age, respectively. Previous measurements of serum lipids had not been made regularly so that the duration of hyperlipemia antecedent to the formation of xanthomata cannot be stated. The degree of hyperlipemia in 3 of the 4 cases was severe, and in them

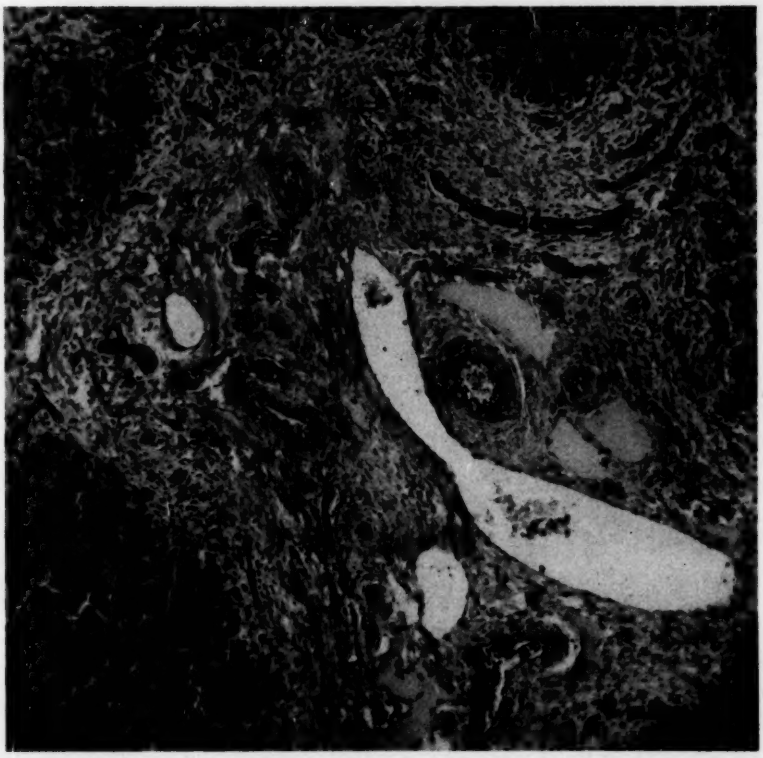


FIG. 7B. See legend on opposite page.

the correlation between degree of hyperlipemia and xanthomatosis was entirely comparable to the larger experience noted above in adult patients with primary biliary cirrhosis. Moreover, in Case 1, a sharp decrease in total serum lipids four months before death was attended by resorption of some xanthomata and diminution in size of others. Presumably a similar change occurred in Patient 3, whose xanthomata largely disappeared before death.

The mechanism of this specific type of hyperlipemia in patients with biliary obstruction is not known. Available evidence pertinent to this question has been discussed in another communication[13] in which it was suggested that the lipids are over-produced rather than under-excreted or under-utilized, and that the site of this over-production probably is the liver. In the terminal stage of biliary cirrhosis, whether primary or secondary, the liver's ability to synthesize lipids fails along with other signs of functional failure. At this stage a decrease in the level of serum lipids is often dramatic and is followed by resorption of xanthomata of the skin.

3. Absence of Intrahepatic Bile Ducts: Absence of biliary epithelium in all sections of hepatic tissue has been noted in the individual case reports above. The extent of tissue available for this search can be evaluated from the following counts of portal spaces in different blocks of tissue: Case 1: (biopsy) 12, (autopsy) 97, 114, 62, 85, and 91; Case 2: (biopsy) 7; Case 3: (autopsy) 72 and 62; and Case 4: (autopsy) 70 and 62. All these

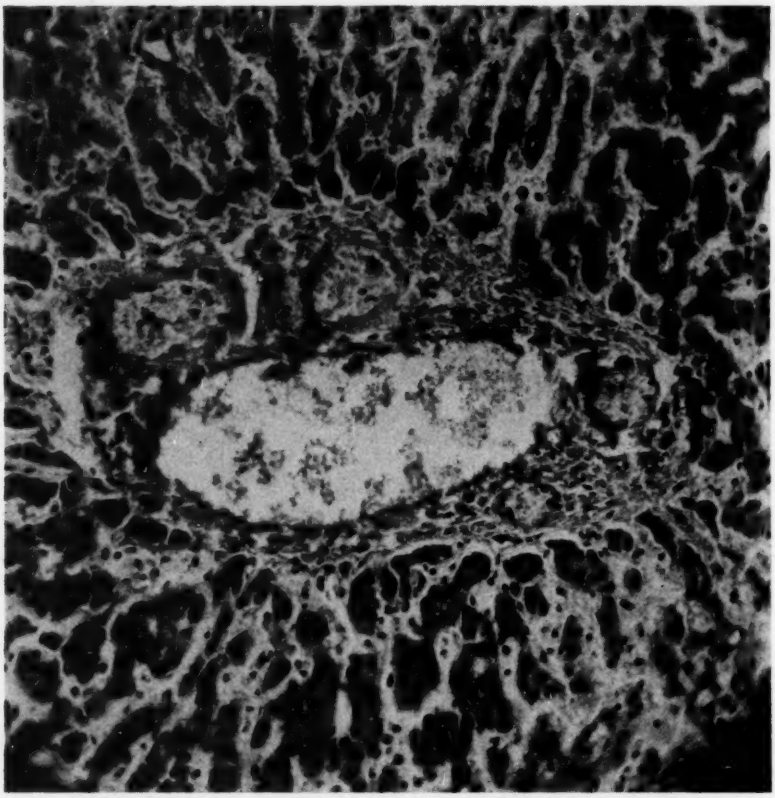


FIG. 8A. Case 1. Medium-sized portal area containing arteries and large vein but no bile ducts. Increased fibrous tissue without leukocyte infiltration in portal area and lobule periphery shows invasion by fibrocytes. Large bile plug is seen at lower right corner. H and E. x195. B (opposite page). Control case—congenital atresia of extrahepatic bile ducts. Same stain and magnification. In addition to blood vessels, there are numerous bile ducts of cholangiolar type. All hepatic cells contain bile pigments.

portal areas were examined for biliary ducts. Not one large or small bile duct was found in all these sections, nor were there remnants of compressed, chronically inflamed or fibrosed ducts to be seen (Figs. 7 and 8). Portal areas showed varying degrees of fibrosis, but there were no localized collections of inflammatory cells suggesting a burned-out reaction around previously existing ducts. Many bile canaliculi were dilated and plugged with inspissated bile, more at lobular peripheries than centrally, and granules of bile pigments were commonly found in the hepatic cells. Increased fibrous tissue within the lobules was found in all cases, and disorganization of lobular architecture was moderately advanced in all except Case 2. There was no apparent regeneration of hepatic tissue. Hypertrophy and hyperplasia of Kupffer cells with retention of lipoid-like material was seen only in Case 4. The findings in all cases warranted the pathologic diagnosis of biliary cirrhosis[18, 19] despite the absence of biliary epithelium.

Failure to locate biliary epithelium in more than 700 portal areas in these four cases

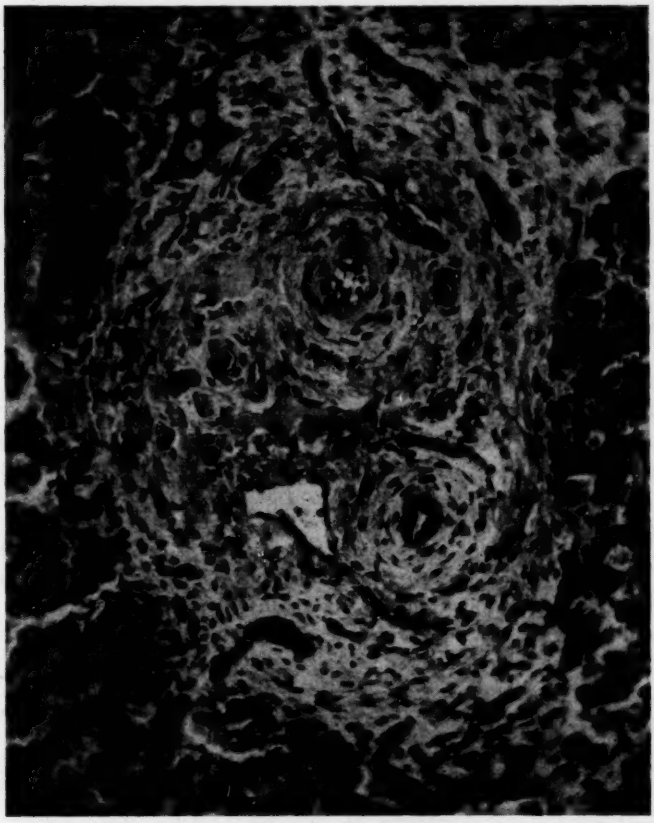


FIG. 8B. See legend on opposite page.

was sufficiently remarkable to have prompted a comparison with representative sections taken at autopsy in a wide variety of diseases of the liver. Study was made of other patients with congenital atresia of the bile ducts (10 cases), Laennec's cirrhosis (10 cases), posthepatitis cirrhosis[20] (5 cases), hepatic plasmacytosis with hypergammaglobulinemia[21] (4 cases), acute hepatic necrosis (2 cases), acute hepatitis (1 case), biliary cirrhosis secondary to common duct obstruction (10 cases), and primary or pericholangiolitic biliary cirrhosis[9, 13, 22] (10 cases). In each of these cases almost every portal area contained more than one bile duct of cholangiolar type, and often there were myriads of them. Large bile ducts with high columnar epithelium also were found in abundance in all categories of liver disease studied.

In the present four cases failure to identify biliary epithelium is rendered more significant by this comparative study, but the probability nevertheless remains that the defect was partial, rather than complete, throughout the liver. The presence of bile-stained ducts in Case 1 and of bile in the gall bladder in Cases 2, 3 and 4 reinforces this belief. The nature of the investigation makes a partial defect least likely in Case 1 where five blocks of tissue in both main lobes were sectioned, but a much stronger possibility in

Case 2 where only seven portal spaces could be studied. The variability of extrahepatic atresias, both in location and extent, suggests that atresia of the intrahepatic bile ducts also may be variable; an all-or-none anomaly need not be expected. Individual differences in clinical behavior would be predicted in the light of these anatomic differences.

In primary biliary cirrhosis, the condition of the small bile ducts is in striking contrast to that of other types of cirrhosis, as well as to that found in the present patients. The most common lesion is a pericholangiolitis[9, 13, 22] with a chronic inflammatory exudate around the smallest interlobular bile ducts. These ducts become compressed and distorted by surrounding fibrosis which extends in an invasive manner into the periphery of the lobule. Due to lack of duplication the cholangioles may be difficult to locate at first glance. However, with search they may be found in all portal spaces. The absence of this picture in the present cases argues against the possibility that the small interlobular bile ducts had become obliterated by an inflammatory process.

4. Embryologic Theories: It is difficult to reconcile embryologic theories with the finding in the present patients of absence of intrahepatic bile ducts. Current hypotheses postulate that hepatic and biliary epithelium are derived from the same endodermal *anlage* in the foregut,[23] the hepatic parenchyma proliferating at the distal ends of the sprouting and dividing bile ducts. Bloom[24] has concluded that the two tissues are finally differentiated by the ingrowth of mesenchyme which extends from the blood vessels to encircle and compress hepatic cords into biliary ducts. On the other hand, Hammar[25] presented evidence from which he concluded that bile ducts and hepatic cells arise from two separate endodermal anlages in the hepatic diverticulum of the foregut. Although often quoted and apparently never challenged, this work has not been substantiated.

If in the course of embryonic development hepatic trabeculae arise solely from biliary structures, absence of bile ducts would imply absence of hepatic cord cells. Yet in the present cases, well-differentiated and grossly normal hepatic tissue was found. Moreover, there are a number of case reports in the literature[5] in which total absence of all extrahepatic biliary tissue was noted despite meticulous dissections of the gastrohepatic ligament and serial sections of this tissue. The presence of fully developed hepatic parenchyma in these two groups of patients can be explained only by postulating that the two tissues, biliary epithelium and hepatic cord cells, grow independently. It is attractive to reason that this independence is an expression of the growth of separate embryologic anlages. Nevertheless, it is conceivable that at an early embryonic stage both tissues arose from a single *anlage,* and that hepatic cells continued to be formed from parent hepatic cells while the development of bile duct epithelium failed for some reason as yet unexplained.

5. Etiologic Factors: Since Thomson's review[1] on congenital obliteration of the extrahepatic bile ducts in 1892, the belief has been held that in the large majority of cases a developmental anomaly was at fault. The anomaly is thought to consist of failure of recanalization of the bile ducts, which during an early embryonic stage appear to be occluded by proliferating duct cells. The frequent association of other congenital anomalies in such cases[5] has been cited in support of this dysontogenetic thesis, while a mass of negative evidence has ruled out congenital syphilis, fetal peritonitis and ascending cholangitis as etiologic factors.

Within recent years Lightwood[26] and Skelton and Tovey[27] have raised the question whether erythroblastosis fetalis may lead in some cases to the same clinical and pathologic

picture as is encountered in true congenital atresia of the bile ducts. It was reasoned that damage to liver cells or hemolysis *per se* might lead to plugging of the canaliculi with bile, and that increased viscidity of the bile was followed by inspissation and obstruction in the larger ducts. This view has been challenged by Lightwood and Bodian[28] and is not supported by the recent pathologic study of Craig.[29] Observations in 16 cases in the last 17 years, to be reported separately,[30] also fail to substantiate this concept.

The current recognition of acute infectious hepatitis in infants[31–34] suggests the concept originally voiced by Rolleston and Hayne[35] in 1901, that injury to the fetal liver may arise from "toxins" carried across the placenta, and that the development of fetal cirrhosis may be followed by descending cholangitis and obliteration of the extrahepatic ducts. It is conceivable that viral hepatitis may be quiescent in the expectant mother and yet cause serious damage to the fetal liver. This hypothesis awaits further investigation, in which it is hoped that the skin-testing antigen recently developed by the Henles and their coworkers[36] may be of assistance.

In 3 of the 4 present cases the co-existence of atresia of the extrahepatic bile ducts with absence of intrahepatic bile ducts supports the belief that a developmental anomaly is the basic defect. In the fourth case, and in two others in the literature (table 1), the finding of normal extrahepatic ducts with absence of intrahepatic ducts fails to support the concept that the large ducts become stenosed when little or no bile flows through them.

6. Surgical Treatment: The fact that less than a dozen successfully operated cases of congenital atresia of the bile ducts have been recorded[37] has prompted increasingly radical surgical approaches. In a recent review Dahl-Iversen and Gormsen[6] stated that in 84% of cases a cholangio-enterostomy is the only feasible procedure. In this operation the open end of the duodenum or jejunum is anastomosed to a wide incision in the inferior surface of the left lobe of the liver, with an enterostomy (Roux-Y) below. Longmire and Sanford[38] have introduced an even more radical approach, in which the left lobe of the liver is sectioned off until a widely dilated bile duct is found. A loop of small intestine is then anastomosed to this duct.

The rationale of such technics is based on the assumption that intrahepatic bile ducts are present and that the ducts of the right lobe communicate with those of the left. The present cases demonstrate that intrahepatic bile ducts sometimes are absent. The hopelessness of undertaking such operative procedures in patients without intrahepatic bile ducts is obvious. It should be axiomatic that a biopsy of the liver must be taken in every case for frozen section and rapid evaluation, as well as for more detailed study after routine fixation and staining. Wedge-shaped pieces of tissue of at least 2 cc. volume should be biopsied from the edge of each main lobe. Histologic signs of obstruction in one lobe but not the other would be strong presumptive evidence of obstruction in the respective hepatic duct. Biopsies should be made immediately after gross inspection of the abdominal viscera and before handling the liver or dissecting the extrahepatic biliary tree.

The technical difficulties of surgery of the bile ducts in the newborn period are easily understood. Advantage must be taken of all procedures which aid in the identification of these small structures. The application of roentgen cholangiography in cases of congenital atresia of the bile ducts was first stressed by Hicken and Crellin.[39] Refinements in technic recently have been suggested by Partington and Sachs.[40] Cholangiography aided in defining stenosis of the hepatic ducts in Case 2. Visual demonstration of bile ducts with ultra-violet illumination after fluorescein injection has been reported recently by

Ménaker and Parker.[41] This technic awaits further evaluation in cases of congenital atresia of the bile ducts.

7. Longevity: Cirrhosis regularly follows unrelieved biliary obstruction.[17] It develops as a sequel to obstruction at the ampulla of Vater, as well as to intrahepatic obstruction at the level of the cholangiole. It is interesting to speculate on the very gradual development of cirrhosis in the present patients and on their prolonged life span, which is in contrast to the more marked derangement of hepatic function and relatively short life span in the usual case of congenital atresia of the extrahepatic bile ducts. Distention of bile canaliculi is common to both types of case, and whatever damage this may cause to hepatic cells should be about equal in severity in each. Since in the present cases there were few, if any, interlobular bile ducts, there could be no distention nor duplication of bile ducts or periductal inflammatory reaction. These abnormalities are typically present in cases of extrahepatic atresia[18] and may be important factors leading in them to the more rapid development of portal fibrosis, lobular invasion and disorganization, and finally of functional failure of the liver.

By what route were the usual components of bile eliminated from the liver in the present patients? Gonzalez-Oddone[42] showed in acute experiments on dogs that ligation of the common duct produced an increase in the bilirubin content of thoracic duct lymph which occurred before that in the blood stream. In most patients with biliary obstruction there is enlargement of lymph nodes in the gastrohepatic ligament with histologic evidence of phagocytosis of bile pigments.[13] This suggests that the lymphatics may act as accessory channels of bile excretion when the normal pathway is blocked.[43,50] The degree to which this adaptive process may take place in different patients might account for some of the variability in severity of jaundice observed in different types of biliary obstruction.

SUMMARY

Case histories of four patients with atresia of the intrahepatic interlobular bile ducts are reviewed. Three of the four also had anomalies of the extrahepatic bile ducts. All had secondary biliary cirrhosis. The course of disease was distinguished by a relatively long life span, all patients surviving more than three years and one remaining alive at five years. Generalized skin xanthomatosis occurred in all patients, together with a marked and characteristic elevation of the serum lipids.

There was no indication on postmortem examination that intrahepatic bile ducts had developed and then become obliterated. The evidence presented in this study suggests that absence of interlobular bile ducts is a developmental anomaly, and that the embryologic development of biliary epithelium is normally independent of the growth of hepatic trabeculae.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to Dr. Richard H. Dobbs, London, and to Dr. Constance Finlayson, Adelaide, Australia, for their generosity in making available essential data and pathologic material pertaining to Cases 3 and 4, and to Dr. Eugene Opie, The Rockefeller Institute for Medical Research, for the generous assistance given in evaluating all pathologic material presented here. It is a pleasure also to acknowledge the cooperation of Dr. Dorothy H. Andersen, Babies Hospital of New York, Dr. Sidney Farber, Children's Hospital, Boston, and Dr. Mary Rothbard, The Rockefeller Institute for Medical Research.

Addendum

P. R., Case 2, 6½ yr. in October 1951, remains in a moderately good nutritional state. In February 1951 serum bilirubin was 3.8 mg./100 cc., phenol turbidity 23 units (1:30 dilution), zinc turbidity 5.6 units, and skin test to the Henles' hepatitis antigen (IH)[36] was negative. Paralleling the fall in serum lipids, skin xanthomata have entirely disappeared. He remains slightly jaundiced and stools contain bile but vary in color. He is doing well in the first grade.

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SPANISH ABSTRACT

Atresia Intrahepatica de los Conductos Biliares

Se revisa la historia clinica de cuatro pacientes presentando una atresia intrahepatica interlobular de los conductos biliares. Tres de los pacientes tenian además anomalías de los conductos biliares extrahepaticos. Todos los pacientes presentaban una cirrosis biliar secundaria. El curso de la enfermedad se distinguió por la duración de vida relativamente prolongada, todos los pacientes vivieron por más de tres años y uno continua vivo a la edad de cinco años. Todos presentaban una xantocromia generalizada de la piel, conjuntamente con una elevación marcada y caracteristica de los lipidos del suero. No se pudo demostrar evidencia patologica alguna que sugiriese que los conductos intrahepaticos estuvieron desarrollados previamente y más tarde obliterados. Se concluye que la ausencia de conductos biliares interlobulares es una anomalía de desarrollo, y que el desarrollo embriológico del epitelio biliar es normalmente independiente del desarrollo de la trabecula hepatica.

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HEAT PROSTRATION IN FIBROCYSTIC DISEASE OF THE PANCREAS AND OTHER CONDITIONS

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DURING the heat wave which occurred in New York City in August 1948, seven children were seen at the Babies Hospital within a space of 24 hours and three more within the week who presented a similar clinical picture. This was manifested by a sudden onset, after approximately 48 hours of hot weather, of marked dehydration, fever and signs of circulatory collapse in the absence of any obvious clinical evidence of acute infection. The major portion of this group was composed of patients who had been previously studied at Babies Hospital and in whom the diagnosis of cystic fibrosis of the pancreas had been established. It is of more than passing interest that one of the patients with heat prostration was found to have previously unsuspected fibrocystic disease.

Observations made during this unusual climatic period in two groups of patients of widely differing age groups have been reported. Cardullo[1] has recorded the response of a large group of children under 2 years of age to the sustained elevation of atmospheric temperature, while Friedfeld[2] during the same period discussed the effects of the heat wave among the residents of the Home of Old Israel in New York City. The types of heat reaction states are clearly discussed and a therapeutic regimen outlined by Friedfeld. Cardullo reviewed the literature, especially with regard to heat prostration in the pediatric age group. He noted that infection, especially of the respiratory tract, predisposed to the development of high fever when patients were subjected to sustained high atmospheric temperature, that this is even more marked in children with congenital or acquired cerebral defects and that in the latter group mortality tended to be high.

OBSERVATIONS AND REPORT OF CASES

The record of daily high, mean and low atmospheric temperatures in New York City during the period under discussion is graphically presented in chart 1. Unfortunately most of the patients included in this report were admitted during a week-end when it was not feasible to obtain many laboratory data. Moreover, many of the children were too ill at the time of admission to warrant any but the most essential procedures. Several cases of heat prostration were observed among inpatients at the Babies Hospital during this period. One of these was a six year old child with fibrocystic disease who was in the hospital at this time for further study and treatment of chronic recurrent asthma. However, the relative frequency of cases of heat prostration with antecedent cystic fibrosis of the pancreas was unexpected and seemed of sufficient interest to be placed on record. Two similar cases have been added to the series during subsequent summers.

Case 1. H. B., 30 mo. of age, was admitted to the hospital on Aug. 28. Initial hospitalization at 10 wk. of age was for investigation of his failure to gain weight. Diagnosis of cystic fibrosis of the pancreas was made after laboratory studies which included assay of duodenal secretions for

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(Received for publication May 14, 1951.)

pancreatic enzymes. During the next 6 mo. he was admitted twice for treatment of respiratory infections. Thereafter he had done well up to the day preceding his present admission when he vomited once. There had been no preceding increase in cough, no diarrhea or other complaints. The morning of admission, he was sufficiently well to visit the zoo. There he began to vomit and continued to vomit everything he ingested up to the time of admission. Examination at that time revealed an acutely ill child who was lethargic and dehydrated. Skin showed poor turgor, had a grayish pallor and felt cold and clammy. Admission temperature was 39.8°C. and PR was 150/min.; respirations were 60/min. and shallow in character. For several hours after admission he remained quite unresponsive, took nothing by mouth and vomited once more. Leukocyte count was 14.8 thousand/cmm. of which 78% were neutrophiles; Hgb. 14 gm./100 cc.; RBC count was 4.45

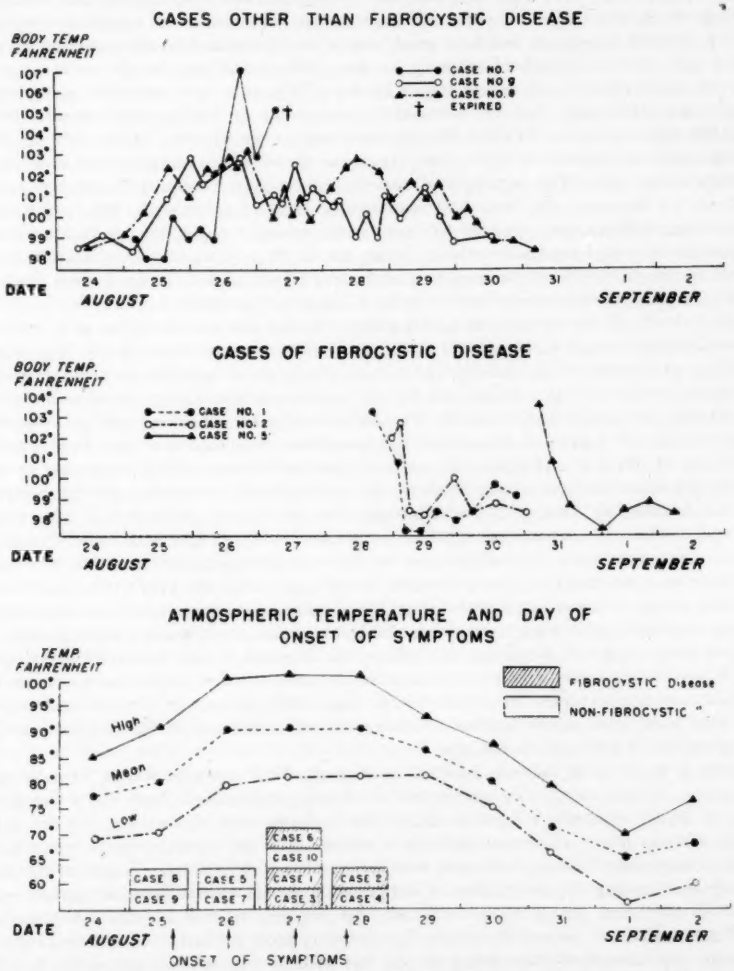

CHART 1. Temperature curves of patients without fibrocystic disease and those with fibrocystic disease as compared with atmospheric temperature. Fibrocystic patients had a later onset of symptoms and more prompt response to therapy. Data for atmospheric temperature were obtained from U. S. Weather Bureau.

million/cmm.; ESR was 12 mm. after 1st hr. (Westergren); total serum protein was 6.3 gm./100 cc.; serum NPN was 60 mg./100 cc. Patient was given glucose solution 2200 cc. and salt-containing fluids 720 cc. followed by whole blood 300 cc. Continuous oxygen was administered and cooling sponge baths were given. Temperature curve is shown in chart 1. Within 12 hr. his temperature dropped to 36.1°C. (it was at this time that blood was given) and gradually over the next 8 hr. returned to normal. During the remainder of his hospital stay, which continued for another 36 hr., temperature never rose above 37.8°C. and he was discharged in 4 days in good condition.

Case 2. W. M., 24 mo. of age, was admitted to the hospital on Aug. 28. First admission occurred when he was 17 mo. old because of recurrent respiratory infections which had started at 2½ wk. of age. Diagnosis of cystic fibrosis of the pancreas was made after extensive investigation. During the months which preceded his present admission, he was hospitalized 4 times for treatment of respiratory infections. Seven weeks prior to his present illness he had been seen in the outpatient service where it was noted that his appetite had been good, and he was maintained on chemotherapy quite well. He had had only 1 to 2 bouts of coughing per day, productive of some mucus but of no purulent matter. He had been well until the morning of the day of admission when he had become irritable and vomited once. His cough had not increased in severity but he had gradually become lethargic. Admission temperature was 39.0°C., PR 140/min., respirations 35/min., weight 10.5 kg. He was severely dehydrated. Skin showed poor tissue turgor and the eyeballs were sunken, yet he was perspiring freely at this time. The remainder of the examination showed nothing remarkable. Leukocyte count was 6.6 thousand/cmm. with 57% neutrophiles, Hgb. 12 gm./100 cc., RBC count was 3.52 million/cmm., ESR 48 mm. after 1st hr., total serum protein 7.8 gm./100 cc. Fluids were given intravenously in a total amount of 2000 cc. during the 1st 24 hr.; in addition he took about 300 cc. of fluid by mouth. Within 12 hr. temperature returned to normal and, except for one elevation to 37.9°C., it remained within normal levels until his discharge on the 4th day.

Case 3. J. Q., 23 mo. of age was admitted Aug. 27. Her first admission was at 13 mo. of age because of failure to gain weight despite a good appetite, the passage of several soft, large stools per day and an intermittent cough since the age of 1 mo. Diagnosis of cystic fibrosis of the pancreas was made on this admission. On a therapeutic diet and prophylactic sulfadiazine she continued to cough intermittently and gained weight slowly. The day preceding her admission, she was seen for her routine visit in the outpatient department. No complaints were elicited at this time. Throat was found to be "mildly red" and presumably was considered as the cause for her temperature of 38.8°C. She was sent home but returned the following day with a history of vomiting and irritability which had been followed by lethargy. She was brought into the hospital wrapped in a woolen blanket despite an atmospheric temperature of 90° as her parents felt she "might catch cold." On admission she was almost moribund, respirations were 50/min. and gasping in character. She was cyanotic; extremities were cold but the trunk was warm. Rectal temperature was 41.6°C. She died within an hour after arrival at the hospital. Postmortem blood culture grew out a paracolon organism. Nose and throat culture yielded Staph. aureus, mannitol and coagulase positive, and a few organisms of the Esch. coli group. Postmortem examination confirmed the diagnosis of cystic fibrosis of the pancreas but failed to reveal any anatomic lesion responsible for the sudden exitus. Unfortunately examination of the brain was not permitted. Pulmonary lesions were chiefly chronic in character and much less severe than usual in fibrocystic patients. There was no evidence of any adrenal or renal abnormality either grossly or on histologic examination.

Case 4. I. G., 6 yr. of age, was admitted on Aug. 17. First admission was at 9 mo. of age for investigation of poor weight gain and attacks of wheezing respirations. There was a strong family history of allergy. Extensive laboratory examination including assay of duodenal enzymes, led to a diagnosis of cystic fibrosis of pancreas and also of asthma. At 14 and 21 mo. of age he was re-admitted because of respiratory infection associated with asthma. It was for the latter complaint that he was again admitted on Aug. 17. Hospitalization and penicillin therapy were followed by marked improvement in his infectional asthma. However, without any preceding signs or symptoms on Aug. 28 (4th day of the heat wave) he was observed to be perspiring most profusely and appeared dehydrated and listless. He vomited 8 times during the day but towards evening, after approximately 1000 cc. of fluid had been given intravenously, he was again able to take and retain oral fluids. At no time preceding his symptoms of heat prostration had his temperature exceeded 38.2°C. He was afebrile on the following day and was discharged.

Case 5. R. A., 4½ yr. of age, was admitted on Aug. 31. At the time of admission he was found to be markedly dehydrated and cyanotic. He was restless, rolled about in bed and had lucid periods which were followed by periods of confusion and irrational behavior. According to admission history, his past medical history had been benign. Present illness started 5 days before admission on the 2nd day of the heat wave when he developed a slight cough, complained of feeling chilly and vomited twice. Vomiting continued intermittently for 3 days. He became pale, listless and his eyes looked sunken to his mother. The night preceding admission, restlessness had become more marked and in the morning speech was incoherent and extremities were cold and blue. He had perspired freely during the night. He had been able to retain fluids offered by mouth. On admission, temperature was 40.°C., PR 120/min., respirations 24/min. He was severely dehydrated and skin was loose and dry. There was moderate cyanosis of lips and of distal parts of extremities. No clinical evidence of acute infection was found. Neurologic examination failed to reveal any meningeal signs, reflexes were slightly hypoactive throughout and sensorium was clouded. Leukocyte count was 12.9 thousand/cmm. with 75% neutrophiles; Hgb. 12 gm/100 cc.; RBC count 3.51 million/cmm., ESR 16 mm. after 1st hr.; CO_2 combining power was 16.8 mEq./l. Fluids were started immediately by intravenous route. Because of restlessness and irritability sedation was given. He continued to have alternating lucid and irrational periods. Within 24 hr., however, he was again responsive, alert and afebrile. On 3rd and 4th days after admission, plasma chlorides were found to be 81 and 83 mEq./l., with a CO_2 combining power of 26.7 and 28.8 mEq./l., respectively. At time of discharge on 9th day, plasma chlorides were 106 mEq./l. and CO_2 combining power was 21.4 mEq./l.

Following discharge, he was seen in the outpatient service where additional pertinent history was obtained. Patient had been having 3 to 4 soft, large, poorly formed stools/day for about 2 yr. and had had a nonproductive cough for about 1 yr. Roentgenograms taken at this time were compatible with diagnosis of chronic bronchopneumonia. He was re-admitted for further investigation. Laboratory studies including assay of duodenal enzymes confirmed the clinical diagnosis of pancreatic fibrosis.

Case 6. J. D., 6 mo. of age, was admitted on Aug. 29. Except for a mild cough which had persisted following a respiratory infection 6 wk. prior to admission, he had been well until 2 days before his admission when he became irritable and refused most of his feedings. On the morning of admission he was found by his physician to have a temperature of 40.5°C. and he received aspirin and penicillin. Past history was significant in that he had frequent foul, mucoid stools and repeated respiratory infections. The referring physician had considered the diagnosis of pancreatic fibrosis and was about to start investigation of this possibility when the present illness intervened. On admission temperature was over 42.2°C. (the thermometer was not calibrated above this level); PR 150/min. and the respirations were 60/min. and shallow. He was an exceedingly obese infant and it was impossible to adequately evaluate his state of hydration and tissue turgor. He was unresponsive and moderately cyanotic. Pupils were pin-point and brief spells of irregular lateral nystagmus were noted. Pharynx was moderately red and some purulent exudate was visible. Fine to medium moist rales were heard in both lungs. Blood culture as well as nose and throat cultures were obtained but these grew out no pathogens. WBC count was 17 thousand/cmm. with 60% neutrophiles. Despite administration of continuous oxygen, intravenous fluids, wet sheet packs and chemotherapy, the patient died 8 hr. after admission. Unfortunately postmortem examination could not be performed as the body was claimed by the medical examiner. It is unlikely that death was due to overwhelming infection in view of the failure to isolate any pathogen from the blood stream or nose and throat. Patient had received only one injection of penicillin before these cultures were obtained. Clinical history is compatible with cystic fibrosis of the pancreas though the definitive diagnosis cannot be made.

Case 7. B. P., 6 mo. of age, was admitted Aug. 23. First admission occurred at 11 wk. of age for investigation of suspected congenital cardiac anomaly which had manifested itself at 6 days of age by enlargement of the heart and a systolic murmur heard all over the precordium. RGs revealed marked cardiac enlargement, especially in the areas of R ventricle and pulmonary conus. ECG showed R axis deviation. There had been no cyanosis, even on crying. Appetite had been poor. No specific diagnosis of the cardiac anomaly was made. About 4 wk. before final admission she became dyspneic and cyanotic. This abated spontaneously in 10 min. She was admitted to another hospital where both cardiac failure and bronchopneumonia were considered in the differential diagnosis. She was placed in an oxygen tent and penicillin was given. Gradually oxygen was withdrawn without reappearance of cyanosis. She was transferred to this hospital for further treatment and again developed dyspnea

and cyanosis while en route. On admission, she appeared to be in some respiratory distress but was not cyanotic. Pulse rate was 160/min.; respirations 44/min. Lungs were clear. Heart was enlarged. A loud blowing systolic murmur was heard best in 4th and 5th ICS 2 cm. to L of midsternal line. Liver had a smooth border and extended about 4 cm. below costal margin. Four days after admission (on 3rd day of the heat wave), patient suddenly became critically ill. Respirations became gasping and skin cyanotic. Lungs were filled with moist rales bilaterally. There was moderate edema of hands and feet. Temperature rose to 42.2°C. Digitalis was given intravenously. She also received penicillin and oxygen but died 24 hr. later. Postmortem examination revealed an interventricular septal defect and congenital mitral stenosis and insufficiency. Lungs showed acute lobular pneumonia.

Case 8. K. B., a male Negro, 6 mo. of age, was admitted on May 28 because of vomiting and failure to gain. He was born after a gestation period of 6 mo. and weighed 2.4 kg. at birth. Vomiting had been persistent and he had been in a hospital almost continuously up to the time of admission to this hospital. On admission, weight was 3.6 kg. He was markedly emaciated with long thin extremities and loose skin. He was alert but showed impaired muscle power and control. A diagnosis of short esophagus with thoracic stomach was made by esophagram. "The esophagus is dilated and short, terminating several cm. above the diaphragm. The short esophagus is continuous with the stomach which protrudes through the esophageal hiatus and extends into the thorax for a distance of several centimeters. The terminal segment of the esophagus appears to be stenotic and the esophagus above this point is dilated as well as short." The esophagus was dilated and gastrostomy was performed in order to permit more adequate feeding. However, vomiting continued although with less severity and he gained weight slowly. He had been afebrile when suddenly on Aug. 25 (the 2nd day of the heat wave) his temperature rose to 39.4°C. There had been no preceding change in his clinical state. No clinical evidence of infection was found. Leukocyte count at this time was 8.3 thousand/cmm. with 25% neutrophiles, and a chest RG was normal. He was started on penicillin and sulfadiazine but his temperature remained elevated until Aug. 31 (the last day of the heat wave) when it returned to normal and remained so.

Case 9. M. D., 28 mo. of age, was admitted on Aug. 6, 2 days after discharge from another hospital where she had spent most of her life. A diagnosis of esophageal atresia and tracheo-esophageal fistula had been made shortly after birth and a gastrostomy had been done. Attempts to construct an external esophagus along the anterior chest wall had been unsuccessful. However, reconstruction of an esophagus in the posterior mediastinum was accomplished. Following the latter procedure, a broncho-esophageal fistula and a lung abscess developed, both of which drained through the thoracotomy incision. Jejunostomy had been performed and feedings were given both by gastrostomy and jejunostomy. In all she had been subjected to over 30 different surgical procedures. She was admitted to this hospital because of vomiting and fever of 40.0°C. She was small, pale and poorly nourished and appeared acutely and seriously ill. Within 24 hr. after admission following institution of adequate hydration and chemotherapy, her temperature returned to normal levels and remained so until Aug. 25 (the first day of the heat wave) when her temperature again rose to 39.7°C. and she appeared acutely dehydrated and critically ill. She vomited several times and had 2 loose stools. Despite adequate hydration her temperature remained elevated for the remainder of the heat wave (until Aug. 30) when it again became and remained normal and she began to gain weight slowly.

Case 10. S. E., 22 mo. of age, was admitted on Aug. 30. Three days before admission she had become irritable and refused most of her feedings. There had been no vomiting, diarrhea, cough or convulsions. Past history revealed that she had required resuscitation after a full term spontaneous delivery. She failed to gain weight well or to develop normally. At 22 mo. of age she was unable to sit up or roll over. On admission she appeared dehydrated, comatose and seriously ill. Temperature was 40.5°C., PR 150/min. and respirations 25/min. and irregular in character. No evidence of acute infection was noted except a small amount of sticky exudate between the eyelids. Pupils were small and responded poorly to light. Leukocyte count was 11.7 thousand/cmm. with 53% neutrophiles, Hgb. was 10 gm./100 cc., RBC count was 2.92 million/cmm., urinalysis and examination of spinal fluid were normal both chemically and bacteriologically. Tuberculin skin test was negative. Despite continuous intravenous fluids for a period of 3 days, she showed little clinical improvement. Temperature returned to normal on 3rd day but promptly rose again. At about this time she began to have generalized convulsive seizures. Chemotherapy had no effect on temperature curve. By the 5th hospital week she finally became afebrile but remained unresponsive and unable to take feedings so that

constant gavage feedings were necessary. This case illustrates the profound and, in this instance, apparently irreversible effect of sustained elevation in atmospheric temperature in a patient with cerebral hypoplasia.

Case 11. P. H. At 24 hr. of age this patient underwent operation for meconium ileus at another hospital. From the 3rd postoperative day onward he passed normal-looking stools. Because of vomiting the formula was changed several times. At the age of 1 mo. in the heat wave of August 1949 he became irritable, cried a great deal and had a temperature of 40.0°C. He was admitted to the other hospital where, following a clysis, temperature returned to normal. His weight gain was slow and he developed a persistent cough. At 6 mo. of age he was admitted to this hospital where assay of duodenal enzymes showed absence of trypsin. At this time he appeared well developed and chubby though somewhat small for his age. Respirations were rapid and a few medium rales were heard in the chest. He received antibiotics and an appropriate diet. When examined again at 10 mo., chest was clear. At 11 mo. of age (June 1950) he was admitted to another hospital for treatment of pulmonary infection and dehydration. He was treated with chemotherapy and fluids and did well for about 6 wk. when in another heat wave he developed a temperature of 40.0°C. without any evidence of superimposed acute infection. He responded to parenteral fluid therapy and has done well since that time.

Case 12. B. H., 23 mo. of age, was admitted on Aug. 15, 1949. Patient was delivered by cesarian section. Intestinal obstruction which developed shortly after birth required surgical intervention for meconium ileus. She did well until about 4 mo. of age when she developed frequent coughing spells. Subsequently she had 3 further admissions to this hospital for treatment of respiratory infections. She had been doing fairly well up to 3 wk. before present admission when she developed anorexia and became irritable, weak and easily fatigued. She improved during 2nd wk. but then again developed anorexia and vomiting. This occurred in the absence of any increase in cough, diarrhea or other complaints. Examination on admission revealed a chronically ill child who was lethargic and dehydrated. There were no other significant findings and no evidence of an acute infectious process. Leukocyte count was 8.9 thousand/cmm. of which 53% were neutrophiles; Hgb. 14.5 gm./100 cc.; RBC count was 4.4 million/cmm.; ESR 10 mm. after 1st hr.; serum NPN was 62 mg./100 cc.

Blood chemical findings on admission revealed plasma Na 130 mEq./l.; K 2.7 mEq./l.; plasma Cl 59 mEq./l.; CO_2 combining power 52.4 mEq./l.; serum albumin 5.0 gm./100 cc.; serum globulin 3.4 gm./100 cc. Urinalysis showed pH 5.5; specific gravity 1.020, albumin 1+, 8 to 10 leukocytes/hpf and a moderate number of granular casts.

She was started on salt-containing fluids intravenously and also received saline as well as ammonium chloride by mouth. Within 24 hr. her condition had improved. Blood chemical determination 72 hr. after admission showed a plasma Na 132 mEq./l.; Cl 100 mEq./l.; CO_2 combining power of 28.8 mEq./l.; serum NPN 43 mg./100 cc.

At time of discharge 5 days after admission she appeared cheerful, her appetite had improved and she was no longer vomiting. She was considered to represent a case of protracted heat prostration with marked chloride loss.

Discussion

During the sustained severe heat wave of August 1948, 10 patients were seen at Babies Hospital with signs and symptoms of heat prostration and five of them were infants or children with cystic fibrosis of the pancreas. These five formed an estimated 15% of a series of patients with fibrocystic disease who were in the New York area at the time. This observation suggested that patients with fibrocystic disease of the pancreas are especially susceptible to heat prostration. Sensitized by this experience, the authors have been able to collect two further similar cases during the subsequent two summers. In the light of these recent experiences it is of interest to note that some 10 years ago, prior to the advent of antibiotics other than the sulfonamides, several children with cystic fibrosis of the pancreas were taken to areas where warm weather was more constant in order to minimize exposure to respiratory infections. Several of these children died soon after this move, and as a group they did far worse than those who remained in a cooler

climate. This clinical observation was unexplained but was sufficiently striking to lead the authors to advise against such a move. The untoward effect of sustained high atmospheric temperature on these children now appears a probable though unproven explanation.

A survey of the records of all 10 children observed during 1948 shows that while five and possibly a sixth had fibrocystic disease, the other four formed a miscellaneous group. Two of the latter had recently undergone surgery of the gastrointestinal tract but were in no acute distress prior to the hot weather. The patient described as Case 6, who died shortly after admission, had been suspected of having fibrocystic disease of the pancreas by the referring physician but confirmation or disproof of this impression was not possible. Of the remaining two patients one had cerebral hypoplasia and the other a congenital cardiac anomaly with cyanosis. In comparing the two groups, the infants without fibrocystic disease showed a febrile response earlier in the course of the heat wave than did the patients with cystic fibrosis of the pancreas. This apparently occurred despite a fluid intake considered to be adequate and in spite of chemotherapy. Vomiting was a prominent symptom in only one of the first group.

All five of the patients with fibrocystic disease were considered to be doing well at the time of onset of the heat wave. One (Case 5) was considered a well child and his pancreatic deficiency was not discovered until a subsequent admission. In all five, onset was sudden, with vomiting and irritability. This soon changed to lethargy and in one patient to coma. All showed marked dehydration and early signs of circulatory collapse without evidence of acute infection. In view of the current concept that fibrocystic disease is associated with a widespread abnormality of epithelial glands, it is of interest that two of the patients (Cases 2 and 4) were perspiring profusely at the time of admission. In only one of the group had heat loss been deliberately interfered with. This was the patient (Case 3) who was admitted wrapped in a heavy wool blanket in spite of an atmospheric temperature of over 90°F. This patient had a temperature of 42.2°C. and was the only one of the group with pancreatic fibrosis to succumb. Her situation was comparable to that of a surgically draped patient in a hot operating room, a circumstance which has often been observed to result in hyperpyrexia.

The response of the patients with fibrocystic disease to adequate hydration was prompt in the four survivors. The temperature became normal within 24 hours after institution of therapy and remained so. Oxygen was administered in two cases and physical means such as cool sponges and electric fans were also employed.

It is not clear why vomiting should be the initial symptom but it appears to contribute to the disturbance in body chemistry. The hypochloremia observed in the two patients in whom blood chlorides were studied may be considered partly the result of vomiting and partly due to loss of chlorides by sweating. In Case 5, the plasma chlorides were 81 and 83 mEq./l. on the 3rd and 4th days of hospitalization and the levels did not rise to normal until the 9th day. The patient last observed, Case 12, had been vomiting prior to her heat prostration and had a plasma chloride level of 59 mEq./l. and a CO_2 combining power of 52.4 mEq./l. Within three days of treatment of her dehydration the chloride level rose to 101 mEq./l. and the CO_2 combining power fell to 28.8 mEq./l.

Two hypotheses may be considered as an explanation for the susceptibility of patients with cystic fibrosis of the pancreas to heat prostration during prolonged high atmospheric temperatures. The first has been mentioned, that the sweat glands, as well as the glands

of the pancreas and other organs, are inadequate in function. However, all patients were dehydrated on arrival at the hospital and two were observed to be sweating profusely. A relative deficiency of the ability to sweat is a suggestion which should be held lightly until supported by quantitative data. An alternative hypothesis, that a low-grade infection was present which was sufficient to increase metabolism but not to produce fever under ordinary circumstances, seems more probable. This may be conceived as resulting in a lowered margin of tolerance to increased external temperatures.

These observations appear to have two clinical applications. In the first place, a known fibrocystic patient should not be subjected to high atmospheric temperatures when this can be avoided, and should be supplied with large amounts of fluids and additional salt when high temperatures cannot be escaped. Secondly, infants and young children without other recognized disease who succumb to heat prostration should be surveyed with the possibility in mind that previously unsuspected pancreatic deficiency may be present.

Summary and Conclusions

Twelve cases of heat prostration in infants and children are reported. Ten of these occurred during the New York City heat wave of August 1948.

Seven of these patients had cystic fibrosis of the pancreas. These patients differed from those with heat prostration but without fibrocystic disease in the following ways: They were considered to be doing well prior to the acute onset; the onset was later in the course of the heat wave than was the case in the nonfibrocystic patients; onset was with vomiting; the clinical response to therapy was prompt while the return of plasma chlorides to normal was more gradual.

Patients with fibrocystic disease of the pancreas are especially susceptible to heat prostration during prolonged periods of high atmospheric temperature. This fact has a practical application in prophylaxis for known cases of this disease, and in arousing a suspicion of the disease in infants and children with heat prostraton who have previously been considered healthy.

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Spanish Abstract

Postración Debido al Calor en Casos de Enfermedad Quística Fibrosa del Pancreas y otras Condiciones

Durante la ola de calor que afectó la ciudad de New York en Agosto de 1948, diez casos de postración debido al calor fueron observados en el Babies Hospital en un periodo de una semana. El cuadro clinico de estos casos se caracterizó por un comienzo abrupto, fiebre, vómitos, irritabilidad, deshidratación marcada y signos de colapso circulatorio en ausencia de signos clinicos obvios de infección aguda. Cinco de los diez pacientes eran niños en los cuales el diagnóstico de enfermedad quística fibrosa del pancreas fué establecido durante admisiones previas al Babies Hospital. Todos gozaban de buena salud con anterioridad a la ola de calor. El tratamiento consistió en la hidratación adecuada, oxigeno y baños de esponga fríos. La repuesta al tratamiento de los pacientes con la enfermedad quística fibrosa del pancreas fué rápida en cuatro casos; la temperatura bajó a los niveles normales en las primeras 48 horas. El único paciente con enfermedad quística fibrosa del pancreas que falleció, fué admitido al hospital envuelto en una colcha de lana a pesar de una temperatura de 42.2 grados Centigrados; falleciendo a la hora de haber sido admitido. De los otros casos, uno

presentaba una malformación congenita del corazón, dos pacientes habian sido operados recientemente del aparato gastrointestinal pero no estaban enfermos con anterioridad a la ola de calor; el otro paciente presentaba una hiperplasia cerebral. En este grupo la repuesta al tratamiento fué menos rapida y los síntomas solo fueron aliviados al final de la ola de calor. Dos casos adicionales de postración debido al calor fueron observados en los dos veranos sucesivos, ambos pacientes sufrian de la enfermedad quística fibrosa del pancreas.

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SPLANCHNICECTOMY FOR PANCREATIC FIBROSIS

Analysis of Results in 24 Patients

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SINCE a preliminary report[1] by the present authors concerning the early effects of splanchnicectomy for pancreatic fibrosis (mucoviscidosis), this operation has been performed on 24 patients six or more months ago. It would seem that sufficient time has now elapsed to permit reasonable evaluation of this procedure. The purpose of this paper is to record observations on the more permanent effects of splanchnicectomy in these 24 patients.

Originally, it was thought that the impaired pancreatic function characteristic of this disease might be due in part to a cycle of poor circulation, ischemia and fibrosis of unknown origin and that improvement in circulation by means of splanchnicectomy might to some extent "revive" any residual functional pancreatic tissue. In other words, it was hoped that progress of the fibrosis might be interrupted by improving the local blood supply to the pancreas. This hope was strengthened by results obtained in the first child thus treated. In this patient a real increasing output of trypsin was demonstrated after splanchnic block with procaine, and again following right splanchnicectomy. However, no such increase in trypsin has been observed in any other patient in the series, though in several there was transient or rather prolonged improvement in the general status and particularly in the respiratory component of the disease. In some patients improvement in this latter regard was so sudden and dramatic following splanchnicectomy that it could hardly be attributed to any conceivable change in pancreatic function *per se*. It was, therefore, necessary to consider other explanations for these changes, such as reflex patterns.

The presence of viscero-visceral reflex arcs has been demonstrated;[2] for example, it is known that stimulation of various abdominal viscera can cause bronchospasm. Such reflex arcs are apparently mediated through the reticular area of the brain stem. Accordingly, it seemed conceivable that a progressive lesion of an abdominal organ, such as mucoviscidosis of the pancreas, might result in a state of autonomic dyskinesia, causing more or less persistent bronchospasm and bronchorrhea. If this were true, then interruption of splanchnic nerves to the pancreas might be expected to affect such a reflex arc simply by breaking its afferent limb.

SELECTION OF PATIENTS

In all 24 patients a diagnosis of mucoviscidosis was established according to conventional criteria. As indicated in table 1, all but 4 patients were less than 48 mo. old at the time of operation; the average age at operation was 30 mo., with a range of from 3 to 81 mo. Definite symptoms attributable

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Presented before the American Pediatric Society, Atlantic City, May 4, 1951.
(Received for publication April 19, 1951.)

TABLE 1

PERTINENT DATA IN 24 PATIENTS WITH MUCOVISCIDOSIS TREATED BY SPLANCHNICECTOMY

			At Time of Operation			Interval Since Operation		Status*		
Order	Patient	Sex	Severity†	Duration of Symptoms, Mo.	Age, Mo.	To Antibiotic Therapy, Mo.	To Death or to Present, Mo.	a. After Splanchnic Block	b. After Splanchnicectomy 1st. 2 wk.	c. After Splanchnicectomy Beyond 2 wk.
1	J.F.	M	S	70	72	5	19	I.	I.	I.
2	M.G.	F	M	12	17	7	19	N.C.	E.	E.
3	G.G.	F	M	22	27	7	18	N.C.	N.C.	N.C.
4	M.A.	M	S	38	42	—	0(d)‡	E.	—	—
5	C.H.	M	M	24	24	4	18	I.	I.	I.
6	J.S.	F	S	40	40	½	17	N.C.	I.	E.
7	C.H.	M	S	23	23	—	1/15(d)	—	—	—
8	P.J.	F	M	43	48	6	17	—	E.	N.C.
9	P.N.	F	S	7	13	½	6(d)	—	N.C.	—
10	R.P.	F	S	44	60	½	12(d)	N.C.	N.C.	—
11	D.B.	F	M	4	5	2	13	I.	E.	E.
12	T.C.	M	M	15	15	5	13	I.	E.	E.
13	K.S.	F	M	2	3	½	10	—	E.	E.
14	C.H.	F	S	5	5	9	9	I.	E.	I.
15	A.G.	F	S	55	81	0	½(d)	N.C.	—	—
16	C.B.	F	M	51	60	2	8	—	N.C.	N.C.
17	K.W.	F	M	18	18	?	8	N.C.	N.C.	?
18	A.M.	F	M	24	24	3	7	—	N.C.	E.
19	B.J.	M	M	24	24	½	3(d)	—	N.C.	—
20	M.N.	F	S	18	18	1	7(d)	—	E.	—
21	K.L.	M	S	18	18	½	2(d)	—	N.C.	—
22	G.O.	F	S	9	20	½	12	—	N.C.	N.C.
23	K.E.	F	Mi	37	42	1	7	—	N.C.	N.C.
24	J.W.	M	S	36	36	½	5(d)	—	N.C.	—

* I. =improved
E. =equivocal
N.C. =no change
† S =severe
M =moderate
Mi =mild
‡ (d) =died after stated interval

to mucoviscidosis had been present for an average period of 26 mo. before operation, with a range of from 2 to 70 mo. Symptoms had been severe enough to warrant a clinical impression as to the early nature of the disorder before the age of 1 mo. in 15 of the patients. At examination, they all presented the classical clinical appearance of pancreatic fibrosis. Their generally poor nutritional status was reflected by their weights: according to the anthropometric charts of the Boston Children's Medical Center, the weights of only 4 patients fell above the tenth percentile; weights of 5 patients fell between the tenth and third percentile, and those of the remaining 15 were below the third percentile. Only one child lacked definite objective evidence of recurrent or protracted pneumonitis; 8 patients had advanced bronchiectasis and 10 had typical though less advanced pulmonary changes. Definite evidences of pulmonary disease were present in the remaining 5, though roentgenograms did not show more than questionable increases in size and density of the hilar shadows or bronchovascular markings. None of the 24 patients had a positive reaction to the tuberculin test.

In general, it might be said that only one patient had mild manifestations of the disease; at the age of 3½ yr. she had the typical habitus, and no trypsin could be demonstrated in the duodenal contents, though she had minimal respiratory complaints. Eleven patients were considered to have moderately severe manifestations in that they were conspicuously small and had objectively definite and progressive pulmonary disease. The remaining 12 were considered to have severe evidences of mucoviscidosis with more advanced changes in the roentgenograms, or proved bronchiectasis. Only

5 patients had received aureomycin prior to referral for consideration of splanchnicectomy, though all were admitted for this operative procedure after other conventional therapeutic measures apparently had accomplished little. In several cases, the operation was justified by the desperate philosophy, "everything to gain and nothing to lose."

Shwachman's[4] report on the efficacy of aureomycin in controlling the respiratory manifestations of mucoviscidosis appeared soon after our studies were initiated. Because it seemed certain that aureomycin does control many of the secondary manifestations of this disease, it was felt necessary to give the drug to any patient who had continuance or recurrence of any alarming pulmonary symptoms following splanchnicectomy. Consequently, all but one of these patients have been given aureomycin or terramycin after intervals of from 7 days to 7 mo. following splanchnicectomy; this has made final evaluation of the surgical procedure *per se* understandably difficult.

Results

A. General: Although no patients were cured, the early impression was that some were materially benefited. The task of evaluation was complicated by such factors as the well known range in severity of manifestations, the "wishful thinking" of parents and

TABLE 2

Results of Splanchnic Block and Splanchnicectomy in Mucoviscidosis

Result	Splanchnic Block	Splanchnicectomy	
		(in 2 wk.)	(beyond 2 wk.)
Died		3	6
No change	6	11	5
Equivocal	1	7	6
Improved	5	3	3
Unknown	0	0	1
Total	12	24	21

attendants, the variable nature of intercurrent infections, and the efficacy of newer antibiotic agents. In the latter regard, no claim is made for efficacy of splanchnicectomy alone in ameliorating any symptoms beyond the postoperative date when antibiotic therapy was given for any reason whatsoever; intervals from operation to institution of antibiotic therapy are recorded in table 1.

In each case the postoperative status was evaluated on the basis of reports of parents regarding changes in gastrointestinal or respiratory symptoms, general behavior and activity. Toward this same purpose, reports from referring physicians together with the authors' records were carefully perused as to changes in weight, in auscultatory evidences of pulmonary involvement, in RGs and in frequency or severity of respiratory flare-ups. Preoperative and postoperative nitrogen balance studies were completed in two patients.

B. Criteria for Evaluation: Patients were classified as *improved* only if they exhibited definite and progressive gain in weight, increased activity with return to reasonably normal behavior and appreciably less frequent and severe respiratory symptoms. Voluntary reports of parents as to decrease in frequency, bulk and odor of stools could not be corroborated by any objective evaluations the authors could make. In those cases in which improvement was considered *equivocal,* there could be discerned no definite objective evidences to correlate with the uniformly gratifying reports of parents as to minor and

variable improvements in weight, activity or behavior, and reduction in frequency and severity of respiratory complaints.

C. By Stages: The effects of splanchnic block and of splanchnicectomy were, of course, evaluated separately, the latter procedure being evaluated as to early and late effects. The general evaluation of the results in each case appears in table 2; only 12 patients had simple splanchnic blocks, and 21 patients survived the early postoperative period of two weeks to permit evaluation of late results. In general, early and late effects of splanchnicectomy were similar, with the following two exceptions:

Case 14: C. H., 5 mo. old at time of operation, had had severe classical features of mucoviscidosis since the neonatal period. After confirmatory diagnostic studies had been performed, splanchnicectomy was accomplished under rectal pentothal together with local anesthesia; during the 1st 2 wk. postoperatively the gain in weight was only slight, respiratory distress and cyanosis were questionably diminished, and auscultatory evidences of bronchiolitis were not appreciably altered. However, in the intervening 9 mo. since discharge from the hospital, and with no antibiotic therapy, there has been progressive gain in weight and the patient has had no respiratory complaints other than infrequent mild and transient "colds." Thus, an equivocal early result was followed by later apparently real improvement.

Case 6: J. S. had had severe manifestations of fibrocystic disease since the neonatal period, and the diagnosis had first been established elsewhere at age of 4 mo. Following right splanchnicectomy at age of 40 mo., there was remarkable and dramatic clearing of obviously severe bronchiolar obstruction, particularly in the R lung. She gained weight rapidly in the early postoperative period until she contracted a fresh respiratory infection shortly after return home; aureomycin therapy, reinstituted at that time, has been given almost continuously (about 17 mo.). Splanchnicectomy on the L side, done 5 mo. after the first operation, did not appreciably affect objective evidences of progressive bronchiectasis in the L lower lobe. Consequently, the final result was considered to be equivocal despite initial satisfactory improvement.

In the entire series there were 9 deaths, one at the time of operation, 2 in the early postoperative period, and 6 at intervals of from 2 to 12 months following splanchnicectomy. Equivocal evidences of improvement prior to death were observed in only 2 of these 9 patients; one died elsewhere of a respiratory infection 7 months following splanchnicectomy, and the other died 12 months following splanchnicectomy, with classical terminal clinical evidences of cor pulmonale. In both of these children, aureomycin therapy was given during the first month following the operation, so that otherwise gratifying improvement could not be attributed properly to splanchnicectomy alone. Autopsies in 6 of the 9 cases confirmed the clinical diagnoses, advanced pulmonary disease being present in each one; pertussis, poliomyelitis, and Friedlander's pneumonia were the terminal infections in 3 patients.

There were no definite evidences of significant change in the natural course of this disease in 6 of the 12 patients immediately following splanchnic block, in 11 of 24 patients during the first two weeks following right splanchnicectomy or in 5 patients who were observed for periods of 8, 12 and 18 months following operation. Manifestations considered to be only moderately severe before operation in two patients have remained unchanged. Five of the 11 patients considered unchanged in the early postoperative period have subsequently died of the disease; the others have shown no later changes of importance which might be related to the operative procedure.

All but one of 6 patients with equivocal evidences of improvement in the early postoperative period have remained in this same category subsequently. Circumstances for this single exception have already been cited.

Gratifying auscultatory evidences of improvement in bronchospasm and bronchorrhea were noted in 5 of 12 patients immediately following paravertebral splanchnic block with procaine hydrochloride; in only 2 of these 5 was similar improvement observed following splanchnicectomy. In the other three the postoperative changes were equivocal at best. The circumstances in one patient who improved appreciably following splanchnicectomy have already been mentioned; pertinent data for the remaining two who improved are as follows:

Case 1: J. F., a boy 3½ yr. old, almost totally incapacitated by severe respiratory manifestations, was the first patient in the group to be operated upon. Symptoms justifying an impression of mucoviscidosis had been present from the 2nd mo. of life, and bronchographic examination had established the presence of cylindric bronchiectasis a year before splanchnicectomy. All observers agreed that the effects after splanchnic block and later splanchnicectomy were truly dramatic. Following hospitalization, the child remained relatively well and gained weight slowly despite several mild intercurrent respiratory infections; 5 mo. following operation, aureomycin was given for the first exacerbation of respiratory symptoms in any way similar in severity to those which had been practically continuous prior to the procedure. In the remaining 12 mo. since operation he has received almost continuous aureomycin therapy together with all other medical measures usually employed for treatment of fibrocystic disease with bronchiectasis.

Case 5. C. H. had classical symptoms of mucoviscidosis from earliest infancy, with 3 long periods of hospitalization for "resistant" bronchopneumonia before he was 1 yr. old; varying combinations of penicillin and sulfonamides had been used almost continuously from the 10th month of life in attempts at prophylaxis of recurrent respiratory infections. Following the demonstration of remarkable clearing of pulmonary signs after splanchnic block, splanchnicectomy was performed at the age of 24 mo. Manifestations of respiratory disease were then minimal for 3 mo. postoperatively, and for the subsequent 18 mo. he has received only symptomatic measures and occasional injections of penicillin for treatment of transient and relatively mild "common colds."

D. Nutritional Efficiency: Studies of nutritional efficiency were indicated by the need to obtain further data on any measurable changes wrought by splanchnicectomy. Protein was chosen as the substance to be measured for practical reasons and also because of the characteristic inefficiency manifested by these patients in digesting this foodstuff. The studies were not true balances, in that nitrogen intake was not constant and no attempt was made to standardize the diet during the study period. The children were allowed a free choice from about 20 different foods daily. In an attempt to encourage a high protein intake, however, the diet offered consisted of about 30% high protein foods; gross fat was eliminated, because it was felt that it might interfere with digestion of protein. No effort was made to influence the children's choice of foods offered, but sufficient quantities of each food were provided to satisfy appetites completely and actual intakes were carefully evaluated.

TABLE 3

NITROGEN BALANCE STUDIES IN 2 PATIENTS BEFORE AND AFTER SPLANCHNICECTOMY

Patient	Grams N_2 Retained*	
	Preoperative	Postoperative
9. P. N.	−1.6, +1.5, −0.9	−0.2, +0.8, +0.6
10. R. P.	+1.4, +5.7, +4.7	+1.6, +2.8, −0.8

* Each figure represents average value for a 3 day period.

Four analyses over nine day periods were completed for 2 patients, 2 periods preoperatively and 2 postoperatively. Justification for drawing any conclusions from such a small experience is derived from the agreement between the results observed and from apparent confirmation secured by weight-gain in these children and most other patients in the group over a longer period of time.

The values obtained are presented in table 3. As can be seen, there was no apparent change in the ability of these patients to utilize ingested protein.

E. Miscellaneous Relationships: As indicated earlier, results did not appear to be related to age or condition of the patients at the time of operation, though this series contained a high proportion of bad risks for evaluating *any* procedure. Younger patients with milder manifestations of the disease would be difficult to study, in view of the established efficacy of antibiotic therapy. In only one child was there any postoperative increase in trypsin from duodenal contents. Serum levels for amylase, cholesterol, glucose, nonprotein nitrogen, vitamin A or carotene, determined for most patients preoperatively, apparently bore no relationship to outcome. Preoperative correction of varying degrees of anemia and vigorous efforts to combat the recognizable pathogens recovered from the upper respiratory tract beclouded any prognostic considerations along these lines. A detailed discussion of the results of bacteriologic studies in these patients does not fall within the scope of this paper; hemolytic Staph. aureus appeared to be the most frequent organism responsible for the chronic pulmonary infections, and resistant gram-negative encapsulated rods of the Friedlander-Aerogenes type were the apparent offenders in some of the most advanced cases.

Anesthesia was induced with ether by the open-drop method in 18 patients, and with pentothal rectally supplemented with local infiltration with procaine hydrochloride in the remaining six; the total duration of the operative procedures varied from 45 to 125 minutes. Close inspection of the records indicated no correlation of the postoperative results with the type of anesthesia employed or the duration of the operation itself.

Discussion

Despite a number of practical difficulties interfering with objective evaluation of results, 3 of the 24 patients seem to have been materially improved after splanchnicectomy, particularly in so far as the respiratory components of the disease are concerned. The very efficacy of antibiotic agents in these patients has made extremely difficult the task of evaluating results of the operative procedure *per se*. Splanchnicectomy did seem to control many symptoms produced by bronchospasm, at least temporarily, and respiratory distress was appreciably ameliorated in three patients for periods of 4, 5 and 9 months, respectively.

Splanchnicectomy is not a curative procedure, and at present the authors are reserving it for those patients whose symptoms are not reasonably well controlled by competent medical therapy. Splanchnic block has little place in the therapeutic regimen, as it almost always requires the additional hazard of deep sedation or a general anesthetic for such young patients; moreover, the results appeared to correlate poorly with those following splanchnicectomy.

Present observations do not permit any definite opinion as to results of splanchnicectomy done earlier in life or in patients with milder manifestations of the disease; no significant changes were observed in the single child with mild manifestations, and only one of three patients under the age of one year may have been actually benefited by the opera-

tion. It is tempting to believe that the results observed in this group of patients, most of whom had reasonably advanced manifestations of mucoviscidosis, might be improved by selection of better risks for evaluation of this or any other therapeutic procedure. The present investigators are resigned, however, to the conviction that the efficacy of antibiotic agents will make justification for surgical intervention and continuation of studies of this sort, extremely difficult.

Summary

Based on the rationale that splanchnicectomy might interrupt a viscero-visceral autonomic reflex arc responsible for bronchospasm and bronchorrhea, this operation has been performed on 24 infants and children with mucoviscidosis, most of whom were poor operative risks. Three of them died at or soon after operation, and six others have died at intervals of from 2 to 12 months postoperatively. Of the remaining 15, manifestations are essentially unchanged in five, and equivocally ameliorated in six. No information could be secured concerning the late effects in one child (Patient 17, K. W.). Three patients may have been materially benefited by the procedure.

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Spanish Abstract

Splanicectomía en la Enfermedad Quística Fibrosa del Pancreas; Analisis de los Resultados en 24 Pacientes

Veinticuatro niños que padecian de mucoviscidosis fueron sometidos a splanicectomía. La indicación quirúrgica fué basada en el concepto de que la splanicectomía interrunpe el arco reflejo autonómico (viscero-visceral) responsable del bronco-espasmo o de la broncorrea. La mayoría de los casos intervenidos constituían riesgos operatorios pobres. Tres de los casos fallecieron en un corto plazo después de la intervención quirúrgica, y séis más fallecieron a intérvalos entre séis y doce meses despues de la operación. De los quince restantes, cinco han permanecido igual que antes de la intervención y séis han sido posiblemente mejorados. En uno de los pacientes (#17, K. W.) no se pudo obtener la información adequada del postoperatorio. Tres de los niños aparecen indudablemente mejorados después de la splanicectomía.

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PAROXYSMAL HYPERTENSION SIMULATING PHEOCHROMOCYTOMA

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PHEOCHROMOCYTOMA, a tumor rare in childhood, is associated clinically with persistent or paroxysmal hypertension, often with bouts of vomiting.[1] Benzodioxane administered intravenously produces a transient lowering of the blood pressure in patients with this tumor and is considered to be a diagnostic test.[2,3] The authors have observed recently an 8 year old girl with paroxysmal attacks of hypertension and vomiting in whom the administration of benzodioxane induced lowering of the blood pressure. The presence of a pheochromocytoma was strongly suspected, but an extensive exploratory laparotomy performed at another hospital failed to reveal one.

Further study of this patient disclosed several unusual physical characteristics, namely, diminished lacrimation, excessive drooling and sweating and frequent blotching of the skin. A group of children exhibiting these same abnormalities, and suffering from similar paroxysmal attacks of hypertension and vomiting, was recently described by Riley et al.[4] In two of their patients exploratory laparotomy had also been performed in search of a pheochromocytoma, but no tumor had been found. It was considered that their patients represented a previously undescribed clinical entity consisting of an autonomic dysfunction, unrelated to pheochromocytoma. The conformity of the present authors' patient to the pattern described in this group is a confirmation of their observations.

It is worthy of note that a sibling also exhibits the unusual characteristics of diminished lacrimation, excessive drooling and sweating and frequent blotching of the skin, but does not have hypertension or bouts of vomiting. The case reports of these two children follow:

Case 1. J. S., an 8 yr. old Jewish girl, was admitted to Beth Israel Hospital for paroxysmal attacks of vomiting which had occurred since age of 4 yr. She had been born at full term after a long and difficult labor. At birth she was cyanotic, had convulsive seizures and developed a left-sided hemiparesis. Pneumoencephalogram taken at 4 mo. of age revealed considerable right-sided brain atrophy and, although the left-sided weakness disappeared early, the patient had frequent generalized convulsive seizures between ages of 3 and 5 yr. These seizures were controlled by phenobarbital, Dilantin® and Tridione®. During this time there were also numerous attacks of pneumonia, and bronchiectasis was recognized at age of 4 yr.

Despite epileptiform seizures and attacks of pneumonia, the patient developed fairly well and appeared to have average intelligence. She sat up at 6 mo. of age and crawled at 1 yr., but did not walk until 2 yr., 9 mo. of age. Since infancy, it was noted that she never produced tears when crying. Excessive sweating, drooling and frequent blotching of skin were also observed during infancy and these, too, have persisted until the present time.

The first episode of vomiting occurred when the patient was 4 yr. old. A second bout took place 6 mo. later and attacks thereafter recurred with increasing frequency during the subsequent 3 yr.

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(Received for publication June 4, 1951.)

During the 6 mo. preceding the present hospital admission, attacks occurred every 1 to 2 wk. Hypertension, with levels up to 180/130 mm.Hg, was noted during these episodes.

The patient had been studied extensively at several hospitals since the onset of her episodes of vomiting. It seemed probable that she had a pheochromocytoma and an exploratory laparotomy was performed 1 mo. before admission. A pheochromocytoma was not found.

The patient was admitted to this hospital during an acute bout of vomiting. Examination revealed an acutely ill, small, thin girl who was continuously retching and vomiting. BP was 200/110 mm.Hg. Temperature was 38.9°C. Weight was 22.7 kg. Skin was warm and moist with large, irregular, erythematous, macular lesions over the face, neck and anterior chest. She drooled excessively. Right eyelid was red and excoriated and ulcerations of cornea were noted. There was a divergent strabismus and corneal reflexes were markedly diminished. Fundi were normal. Deep tendon reflexes were hypoactive. Numerous large and medium moist rales were heard over L lower lung.

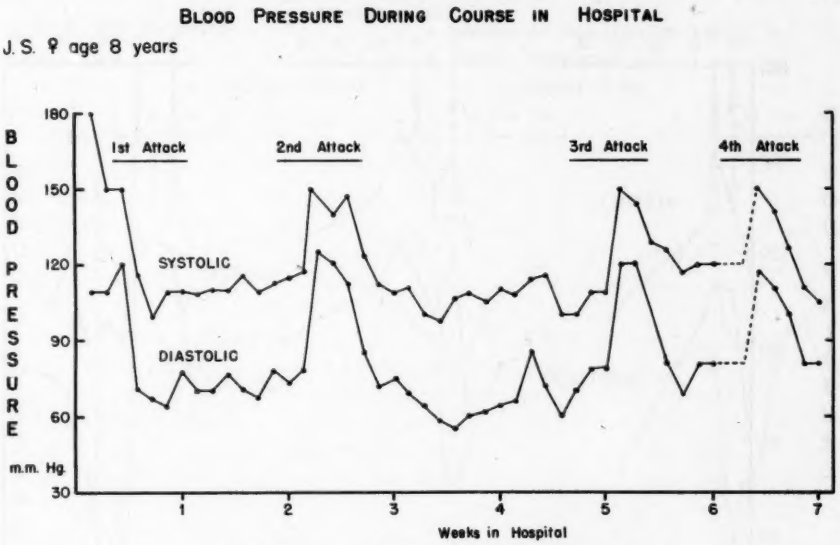

CHART 1. Blood pressure during 4 attacks.

The attack of vomiting lasted 3 days, during which time the BP remained at about 160/130 mm.Hg. Continuous administration of intravenous fluids was required and the patient was irritable and uncooperative. She complained of nausea and abdominal pain and continuously picked at her nose and eyes. On the morning of 4th day she awoke feeling entirely well, ate with a hearty appetite and was friendly and cooperative. At that time BP was 110/80 mm.Hg. She remained well during the next few weeks, BP levels persisting at about 110/80 mm.Hg.

Laboratory tests performed on admission, during the acute attack of vomiting, were as follows: Urine sp. gr. 1.030, a trace of albumin and 4+ acetone. RBC count was 4 million/cmm. Hgb. 11.5 gm./100 cc. WBC count was 14 thousand/cmm. with 65% polymorphonuclear leukocytes. Blood glucose was 111 mg./100 cc., NPN 45 mg./100 cc. and total protein 8.2 gm./100 cc. with albumin 5.8 gm./100 cc. and globulin 2.4 gm./100 cc. Blood electrolytes (mEq./l.) were as follows: Na, 141.6, Cl 100.8, and K 4.3. Electroencephalogram during this attack showed a diffusely slow record which was interpreted as abnormal.

After the initial attack had subsided, urine examination revealed no abnormalities and blood concentrations of erythrocytes and leukocytes remained unchanged as did concentrations of glucose, NPN, Na K and Cl. Urea clearance test was 52% of average normal function. BMR was —2%. ECG was normal. Chest RG showed scattered parenchymal infiltrations at both lung bases. Normal kidney

shadows were seen on films of the abdomen. RGs of long bones and dorsolumbar spine were also negative except for the presence of a small cystic area in the right humerus.

EEGs taken while awake and asleep during a symptom-free period were entirely normal, as were RGs of skull. Pneumoencephalograms performed at another hospital 1 yr. previously also failed to show any abnormalities. Intelligence tests, using the Stanford-Binet scale, revealed a mental age of 7 yr., 9 mo. which corresponded to an I.Q. of 83. A Shirmer tearing test* was performed and this showed markedly diminished lacrimation bilaterally.

Patient remained under observation for a period of 3 mo., during which time she had 6 attacks of hypertension and vomiting (see chart 1). During intervals between attacks of vomiting, when BP

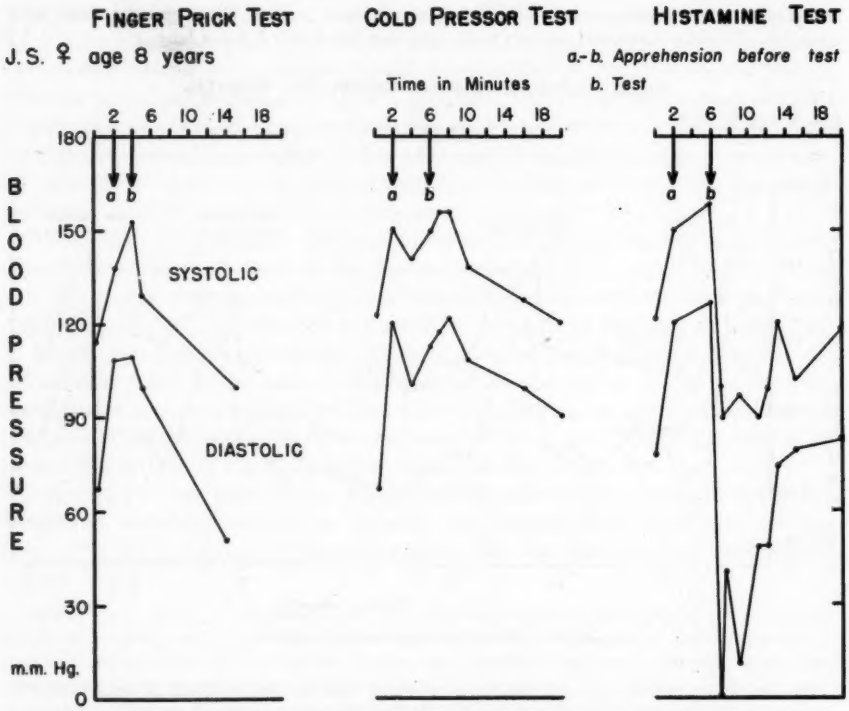

CHART 2. Blood pressure following finger prick, ice water and histamine.

was at a normal level, several procedures were carried out to determine the effects of excitement, ice water and histamine on BP. As an example of the effect of excitement, it was noted that the blood pressure rose during a finger prick from 118/68 to 160/110 mm. Hg. This elevation in pressure was accompanied by obvious apprehension and development of a blotchy rash, both of which disappeared after a few minutes, as BP dropped to normal. A cold-pressor test was next attempted but apprehension was so marked that BP rose from 124/68 to 150/112 mm. Hg just before immersion. BP then remained at 156/118 mm. Hg. during the 60 sec. ice water immersion of hand and finally returned to normal 15 min. later. Histamine test was then performed, with injection intravenously of histamine base 0.025 mg. in 0.25 cc. of saline. BP rose from 122/78 mm. Hg just before venipuncture to 162/128 mm. Hg at the moment the needle entered the vein but just before the injection of histamine was

* Measured strips of #41 Wattman filter paper (5x30 mm.) are placed over lower eyelids after the eyes have been anesthetized with pontocaine. The wetting of at least half of the strip of paper in 5 min. is considered to indicate normal lacrimation.

started. One minute after injection, BP droppd precipitously to 110/0 mm. Hg and then gradually returned to normal in the next 5 min. These changes can be seen in chart 2.

During subsequent attack of vomiting, heavy sedation was given in an attempt to relieve her distress. Although phenobarbital 0.1 gm. given intramuscularly produced drowsiness, it induced no concomitant reduction of vomiting or hypertension.

Since it appeared possible that an undefined autonomic imbalance was responsible for the clinical symptoms, attempts were made to evaluate the effects of adrenolytic and sympatholytic drugs. Benzodioxane® was given intravenously on 3 occasions during 1 attack(chart 3). With each intravenous injection BP fell within 2 min. from levels of about 150/120 mm. Hg to about 110/70 mm.Hg, and then rose to former level during the next 5 min. Since these hypotensive effects were only of short duration, a longer acting sympatholytic agent, Dibenamine®, was studied during a subse-

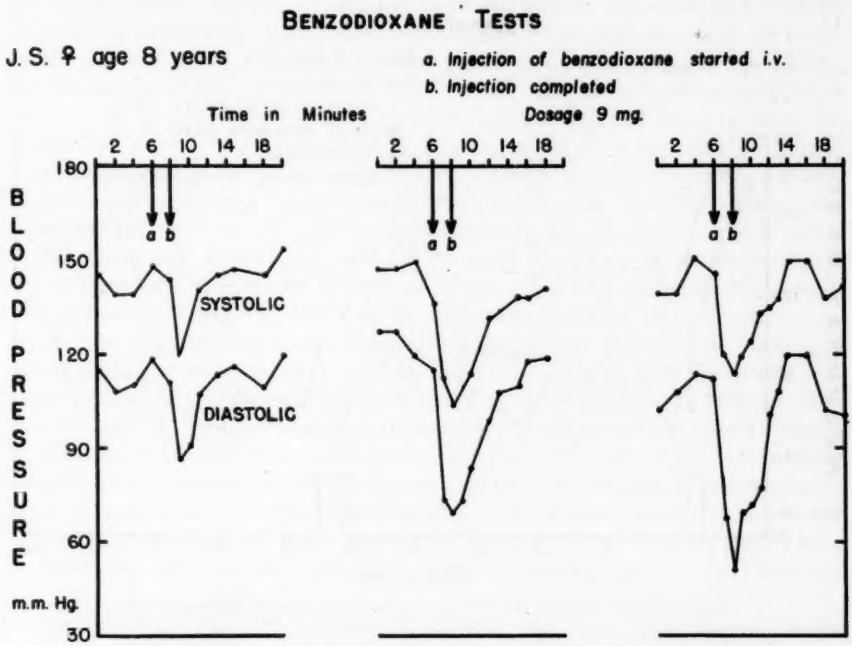

CHART 3. Blood pressure following intravenous injections of Benzodioxane®.

quent attack. An infusion of dibenamine 50 mg. in 200 cc. saline was given slowly intravenously (chart 4). BP fell gradually from 156/122 before the injection to levels around 128/70 mm. Hg in 1½ hr. and remained at about 130/90 mm. Hg for the next 10 hr. Despite this drop in BP, clinical symptoms remained unchanged. The following day the dose of Dibenamine® was increased to 100 mg. and again was given slowly intravenously in a saline infusion. There followed a slight drop in BP but no alleviation of symptoms. It was apparent, then, that lowering of blood pressure had no effect on her associated symptoms.

Since the foregoing agents prcved ineffective in reducing abdominal distress and vomiting, Banthine®, a parasympatholytic agent, was tried next. Administration of large doses of this drug, 200 mg. every 6 hr./rectum for 2 days, did not seem to have any significant effect on the severity or duration of an attack. Eumydrine®, Dramamine®, ACTH and cortisone were also unsuccessful in relieving symptoms. Eumydrine® was given as 0.6% alcoholic solution 30 drops dropped on the tongue every 3 to 4 hr. for 24 hr.; Dramamine® was given as 100 mg. suppositories every 4 hr. for 16 hr.; ACTH was given intramuscularly in doses of 40 mg. every 6 hr. for 24 hr.; cortisone was given intramuscularly, 100 mg. daily for 4 wk. These negative results do not exclude the possibility

that one or more of these agents may have a beneficial effect if administered in a larger dose or over a longer period of time.

Case 2. E. S., a 2½ yr. old Jewish girl, the only sibling of J. S. (Case 1), was admitted for observation and study. The patient had been born at full term after a normal delivery and displayed no cyanosis, convulsions or other abnormalities at birth. However, feedings were taken poorly and were followed by excessive irritability throughout the 1st 8 wk. of life. At that time her evaporated milk formula was changed to Mull Soy® and she has continued to take this soy bean preparation instead of milk. Whenever milk or a milk product was introduced into her diet she was said to develop abdominal cramps, wheezing and a skin rash.

Patient's developmental history was entirely normal. She sat at 5 mo., crawled at 7 mo. and walked at 1 yr. of age. She had no serious illnesses except for 3 attacks of croup. However, there

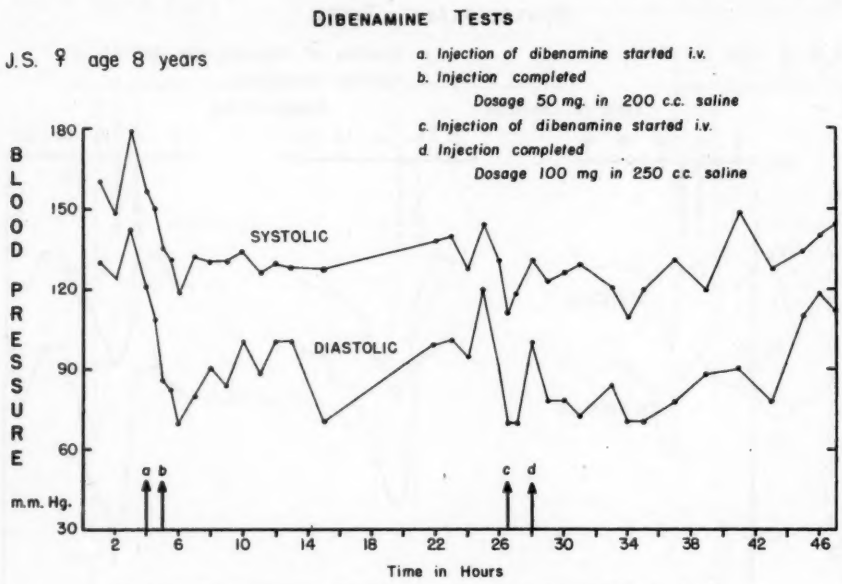

CHART 4. Blood pressure following intravenous injections of Dibenamine®.

were 2 fainting episodes 1 yr. before admission which followed excessive crying. One month before admission there were 3 additional fainting episodes which lasted only a few moments, but which occurred without any known precipitating factors. There have been no convulsive seizures and no bouts of vomiting but she has always been known to cry without tears, to drool and sweat excessively, and to develop transient blotching of skin when excited.

On admission the patient was noted to be well developed and well nourished, in no distress and not appearing acutely or chronically ill. Examination disclosed no abnormalities except for the aforementioned diminished lacrimation and increased salivating and sweating.

Laboratory tests were as follows: Urine was normal with sp. gr. 1.016. RBC was 4.36 million/cmm.; Hgb. 10 mg./100 cc.; WBC 13 thousand/cmm. with 33% polymorphonuclear leukocytes. Fasting blood glucose was 98 mg./100 cc., NPN 31/100 cc., Na 137 mEq./l., Cl 101 mEq./l. and CO_2 combining power, 23.7 mEq./l. A Shirmer tearing test showed diminished lacrimation bilaterally. Skull and chest RGs revealed no abnormalities. EEG was also normal.

Blood pressure readings taken while patient was relaxed ranged around 108/70 mm. Hg. When she became excited, during a venipuncture, a blotchy rash appeared, drooling increased and BP rose to 180/130 mm. Hg. When apprehension subsided, at termination of the procedure, BP fell to 114/80 mm. Hg. There were no vomiting or fainting episodes during the short period of observa-

tion. Four controls, selected from amongst the ward population, showed the following blood pressure changes during an identical test. Their respective BP rose during venipuncture from 100/60 to 140/70, from 100/66 to 140/80, from 104/68 to 130/70 and from 98/60 to 140/96. In all these patients blood pressure changes were accompanied by marked apprehension, but in none was there noted increased drooling, sweating, or blotching of skin, and all cried with tears.

Discussion

The resemblance between J. S.'s clinical picture and that associated with pheochromocytoma is striking. Thus, paroxysmal hypertensive episodes and a response of the hypertension to Benzodioxane® were conspicuous in this patient, as they usually are in patients proved to have this tumor. However, an extensive abdominal surgical exploration of J. S. failed to reveal the presence of a pheochromocytoma. Nearly all pheochromocytomas are found in the abdominal cavity, only two cases having been reported of a thoracic tumor which had produced symptoms.[6] In two of the cases previously reported with symptoms similar to those of the present authors' patient, exploratory laparotomy also failed to reveal the presence of a tumor and at subsequent autopsy on one of them no tumor was found. Furthermore, none of the patients with proved pheochromocytoma have displayed diminished lacrimation, increased drooling or blotching of the skin. Therefore, although the possibility has not been excluded, it appears unlikely that the authors' patient has a pheochromocytoma. In any event, such a tumor could not account for all the symptoms.

J. S.'s syndrome bears a close resemblance to "cyclic vomiting" in its major manifestation, periodicity of vomiting. However, the concomitant symptoms either do not occur in "cyclic vomiting" or have been overlooked.[7] Thus, periodic hypertension might well occur, although not mentioned in cases which are otherwise very well documented. On the other hand, it appears extremely unlikely that excessive drooling and sweating could exist unnoted in "cyclic vomiting," since in this syndrome the patients characteristically have dryness of the skin and mucous membranes during the attacks. It is also improbable that diminished lacrimation, which was so prominent in the authors' patients, could likewise escape notice. Actually, "cyclic vomiting" is an ill-defined clinical entity and may well include cases similar to these. Nevertheless, there are distinct differences which serve to distinguish these patients from those having "cyclic vomiting" as it is commonly seen.

The possibility that J. S.'s attacks of vomiting represented epileptic psychomotor equivalents was also considered, in view of the history of brain injury at birth, an abnormal pneumoencephalogram in infancy, and repeated convulsive seizures from 3 to 5 years of age. However, EEGs at present fail to show epileptiform patterns[8] and the most recent pneumoencephalogram was also normal. Furthermore, psychomotor epilepsy is not known to be associated with hypertension or with evidences of autonomic imbalance, and attempts to alter the progression of the acute episodes in this patient by anticonvulsive drugs have been unsuccessful.

Definitive data concerning the cause of J. S.'s paroxysmal attacks are lacking but it is apparent that she has an unusually labile autonomic nervous system. Instances of comparable autonomic lability have been described in adults with essential hypertension who have intermittent brief outbursts of profuse sweating, increased salivating, blotching of the skin and palpitations, associated with further elevation of the blood pressure ("diencephalic irritation," "hypertensive diencephalic syndrome.")[9-11] However, these patients characteristically displayed increased rather than diminished lacrimation. Similar inter-

mittent attacks of diencephalic activity were described by Penfield[12] in an adult who was found at autopsy to have a tumor of the third ventricle, pressing on the thalamus. Again, as in the "diencephalic hypertensives," increased rather than diminished lacrimation was noted. One other case, reported by Engel and Airing[13] with a clinical picture very similar to that of J. S., including diminished lacrimation, was found at autopsy to have a cystic lesion of the thalamus.

The cause of the autonomic dysfunction in J. S. is not known. The possibility exists that it is a consequence of a diencephalic lesion resulting from birth trauma. However, there was a history of birth trauma in only one of the five similar cases previously reported by Riley et al.[4] In addition, the occurrence of many of the abnormal characteristics of J. S. in her sibling, who had an essentially normal birth and developmental history, suggests that the disorder is not an acquired one. It is of some interest, in this regard, that these children, as well as the cases previously described, have all been Jewish. Whether or not the sibling, E. S., will develop the full syndrome, with bouts of hypertension and vomiting, cannot be predicted, but she now displays a hypertensive response to excitement similar to that of her sister.

Summary

An eight year old child with intermittent attacks of hypertension and vomiting has been described. The blood pressure fell dramatically in response to Benzodioxane®, suggesting the presence of a pheochromocytoma, but this tumor was not found after an extensive exploratory laparotomy. The episodes of hypertension and vomiting together with the associated findings in this child of crying without tears, frequent blotching of the skin and excessive sweating and salivating are considered to be indications of an unusually labile autonomic nervous system. These latter characteristics were present in a younger sibling who also had an extremely labile blood pressure but who did not exhibit periodic attacks of hypertension and vomiting.

A variety of agents were studied for their effects on the patient's signs and symptoms but none of these were demonstrated to have any therapeutic value.

Acknowledgment

The authors are indebted to the late Dr. J. M. Lewis for his suggestions in the study of these patients and in the preparation of this paper.

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SPANISH ABSTRACT

Hipertension Paroxistica Simulando un Pleocromocitoma

Se describe un caso de una niña de ocho años de edad con ataques intermitentes de hipertension arterial y vómitos. La presión bajó precipitosamente en repuesta a la administración de benzodiozane®, sugieriendo la presencia de un pleocromocitoma, pero este tumor no pudo ser demostrado después de una laparotomia exploradora extensa. Los episodios de hipertension y vómitos conjuntamente con otros síntomas asociados tales como la ausencia de lagrimas en el llanto, "blotching" frecuente de la piel, perspiración y salivación excesiva, los cuales son considerados por los autores como manifestaciones clinicas de un síndrome cuya etiología y patología no está bien conocida. Un hermano menor del caso descrito tambien presentaba una alteración similar del sistema nervioso autonómico, pero hasta el momento presente no ha sufrido de ataques de hipertension espontanea o vómitos.

Se estudiaron los efectos de varios agentes adrenoliticos y simpaticoliticos así como tambien cortisona y ACTH sobre los síntomas de este paciente, pero ninguno de ellos demostró tener valor terapeutico alguno.

8 Gramercy Park

VESICULAR PHARYNGITIS

Its Relationship to the Coxsackie Group of Viruses

By J. K. David, Jr., M.D., Daniel Leavitt, M.D., and Beatrice F. Howitt*
Jacksonville, Fla.

DURING the summers of 1949 and 1950, a number of children in Jacksonville, Fla., presented the following clinical picture: The child, usually under 5 years of age, became ill suddenly with fever, malaise and anorexia. Examination revealed vesicular or aphthous lesions on the soft palate and anterior faucial pillars. The fever was of brief duration, usually less than 48 hours. The clinical course of the patients and the appearance of their pharyngeal lesions were strikingly uniform. A viral agent pathogenic for suckling mice was isolated from the throat secretions of 12 of 13 patients showing this clinical picture.

Zahorsky,[1] in 1920, first described a clinical entity of unknown cause closely resembling the illness seen in these patients. His description follows:

"The disease begins suddenly as an acute febrile movement. The temperature often rises to 104 F. A convulsion may occur. Vomiting is often present. Anorexia and prostration are sometimes marked. The throat and posterior part of the mouth show minute vesicles or, if these have ruptured, small punched-out ulcers. They occur on the anterior pillars of the fauces, the tonsils, the pharynx, and the edge of the soft palate. The number of the lesions varies from two to twenty. Dysphagia is often marked. The general and local symptoms disappear in a few days."

Levine, Hoerr and Allanson[2] reported an epidemic of vesicular pharyngitis and stomatitis which occurred in three New Hampshire summer camps. The disease, which affected 106 persons, was characterized by high infectivity and ran a benign course. The chief signs were fever and the appearance of vesicles which subsequently ulcerated on the faucial pillars, soft palate and tonsillar tissue, when present. The authors suggested a herpetic origin of the disease because of the appearance of the lesion.

Breese[3] reported 28 cases of an unusual type of pharyngitis occurring in Rochester, N.Y., in the summers of 1938 and 1940. These cases showed sudden high fever, mild subjective symptoms and inflammation of the soft palate and tonsillar pillars with the appearance of aphthous lesions in the same areas. A single attempt to isolate a virus from the throat secretions of one patient obtained a few hours after onset of the disease was unsuccessful.

Clinical Observations

The present authors' cases were observed during June, July and August. There was definite predilection for young children. Of the 13 patients upon whom viral studies were made, eight were 3 years of age or under, and only one was above 6 years of age. In each patient there was abrupt onset of fever, irritability and anorexia. The older ones complained of sore throat and headache. Within 24 hours of the onset the patient usually felt much better, and fever in most cases had subsided within 48 hours. If the patient was

(Received for publication May 24, 1951.)

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seen early in the disease, inspection of the pharynx revealed from one to a dozen vesicular lesions, 2 to 3 mm. in diameter, on the anterior faucial pillars and the soft palate. The vesicles were surrounded by an areola of intense erythema. A day or so after their appearance the vesicles ruptured leaving small punched-out ulcers in their place. These ulcers persisted for from 3 to 7 days. Three of the patients showed a single vesicle in the anterior mouth. One patient showed several vesicles on the buccal surfaces of the cheeks. There were only two instances of apparent infection in more than one member of a household. One of these (S. C.) was ill with fever of one day's duration before her brother (J. C.) was seen with typical pharyngeal lesions. The mother of B. R. became ill with fever and intense sore throat a few days after his illness.

The usual pattern of the disease is best illustrated by case histories.

C. C., a 4 yr. old girl, became ill in August with fever and headache. She did not complain of sore throat. When seen on the following day, temperature was 38.3°C., and she appeared only moderately ill. Examination was negative except for the pharynx and slight enlargement of submandibular nodes. Several vesicular lesions were present on the anterior faucial pillars. When seen 2 days later she was asymptomatic and pharynx was clear.

B. R., a 4 yr. old boy, became ill with fever and sore throat in July. He had been ill with a typical herpetic stomatitis 15 mo. prior to this illness. He was seen 24 hr. after onset of fever, and at this time numerous vesicular lesions were present on anterior pillars of the tonsils. One vesicular lesion was present on the buccal surface of the cheek. Submandibular nodes were enlarged and tender. Within 48 hr. temperature was normal. Pharyngeal lesions became shallow ulcers and persisted for about 1 wk.

D. H., a 14 yr. old boy, had onset of high fever and headache in June. He appeared ill and temperature was 40°C. when examined on the following day. Examination was not remarkable except for hyperemia of pharynx. High fever persisted for 72 hr. and he complained of sore throat. He was seen 8 days later and at this time numerous small ulcers were present on buccal surfaces of cheeks, soft palate and faucial pillars. This was the only patient who showed more than one lesion in the anterior mouth.

Viral Studies

In the summer of 1949 when the uniformity of the clinical picture presented by these patients was recognized, isolation of virus was attempted in two cases, B. R. and B. P. It was necessary to search for some viral agent other than herpes simplex because one of these patients, B. R., had been observed in a typical attack of herpetic stomatitis one year previously. This disease, which is characterized by systemic illness as well as the appearance of vesicular and aphthous lesions on the mucous membrane of the anterior mouth, may cause similar lesions in the pharynx. It has been shown that this disease represents the initial infection of the host with the herpes simplex virus. It is generally agreed that the disease is not recurrent.

Viral studies were carried out by one of the authors (B. H.) at the Communicable Disease Center, Virus and Rickettsia Section, in Montgomery, Ala. Specimens of throat swabbings and feces were quick frozen and forwarded to the laboratory by air mail. This material was treated with antibiotics and inoculated into suckling mice by the combined intracerebral, intraperitoneal, and intramuscular routes. A viral agent was recovered from both the feces and the throat secretions of the patients, B. R. and B. P. This agent proved to be similar, but of a different serologic type to the virus first isolated in 1948, by Daledorf and Sickles[4] and later designated as Coxsackie virus from the town in New York where it was first recovered. Subsequently the Coxsackie virus has been divided into Groups A and B and also into a number of serologic types within the groups. All of them are

TABLE 1

Patient Age Date Onset	Duration Fever	Subjective Symptoms	Location and Description of Lesions	Duration of Lesions	Contacts Who Became Ill	Isolation of Virus	
						Throat	Stool
S.S. 16 mo. 8-15-50	72 hr.	fever, irritability, anorexia, moderately ill, temp. 40.0°	vesicles on anterior faucial pillars	4–5 days	none	+	−
J.T. 2½ yr. 8-2-50	48 hr.	fever, anorexia, irritability, moderately ill, temp. 37.8°	vesicles on anterior faucial pillars; submandibular nodes slightly enlarged			+	+
M.K. 6 yr. 8-21-50	48 hr.	fever, dysphagia, not ill, temp. 37.3°	vesicles with surrounding erythema on palate anterior and posterior faucial pillars and buccal surfaces cheeks	5 days	none	+	+
T.P. 2½ yr. 7-26-50	72 hr.	fever, irritability, temp. 39.4°	vesicles on anterior faucial pillars	4 days	none	−	−
D.H. 14 yr. 6-20-50	72 hr.	fever, headache, slight cough, very ill, temp. 40.5°	vesicles on anterior faucial pillars and on buccal surfaces of cheeks observed 1 wk. after onset of illness	?	none	+	−
P.M.C. 3 yr. 7-21-50	24 hr.	fever, chilliness, sore throat, moderately ill, temp. 38.1°	vesicle on lip m.m. vesicles with surrounding erythema on anterior faucial pillars and soft palate	1 wk.	none	+	+
P.C. 4 yr. 6-1-50	48 hr.	fever	vesicles; anterior faucial pillars		none	+	+
B.B. 15 mo. 6-16-50		fever, irritability, cough and gagging, vomiting, jitteriness, temp. 38.3°	vesicular lesions on anterior faucial pillars and soft palate			+	0
C.C. 4 yr. 8-28-50	48 hr.	fever, headache, temp. 38.3°	vesicular lesions on anterior faucial pillars and surrounding erythema	3 days		+	−
J.C. 1 yr. 7-8-50	48 hr.	fever, irritability, temp. 39.4°	vesicles; anterior faucial pillars	?	sister	+	+
B.P. 15 mo. 7-4-49	48 hr.	fever, moderately ill, temp. 40.0°	vesicular lesions on anterior faucial pillars; submandibular nodes slightly enlarged	4 days	none	+	+
B.R. 4 yr. 7-5-49	48 hr.	fever, sore throat, temp. 38.9°	hyperemic pharynx vesicles on anterior faucial pillars; 1 vesicle buccal surface cheek	7 days	mother	+	+
N.H. 3 yr. 6-27-50	48 hr.	fever, sore throat, temp. 40.0°	hyperemic pharynx vesicles on anterior faucial pillars	5 days		+	0

CODE
+ positive results
0 negative results
− not tested

Typing of Patients' Viruses Against Antisera

Types 1	2	3	4	5	Group B	Donald H.	Jeffery C.	Results
0	0	0	0	0	0	0	+ weekly	throat swabbings ?
0	0	0	+	0	0	+	0	throat swabbings Type 4
0	0	0	+	0	0	0	0	throat swabbings Type 4
−	−	−	−	−	−	−	−	
0	0	0	+	0	0	+	0	throat swabbings Type 4
0	0	+	0	0	0	0	+	throat swabbings Type 3
0	0	0	+	0	0	+	0	feces Type 4
0	0	+	0	0	0	0	+	throat swabbings Type 3
0	0	0	0	0	0	0	0	throat swabbings ? was neutralized by B. B. antiserum
0	0	+	0	0	0	0	+	throat swabbings and feces Type 3
0	0	0	0	+	0	−	−	throat swabbings and feces Type 5
0	0	0	0	+	0	−	−	throat swabbings and feces Type 5
0	0	+	0	0	0	+	0	throat swabbings Type 3

pathogenic only for suckling mice and hamsters and do not affect the older animals. After inoculation an extensive paralysis appears in 2 to 10 days followed by death of the animal. Widespread pathologic changes are found in the skeletal muscles after injection with the Group A viruses while more neurologic but less extensive muscle damage is found with those of Group B. The muscle pathology begins as a hyaline degeneration of the fibres and progresses to extensive necrosis and calcification.

In the summer of 1950, viral studies were performed on 11 additional patients with vesicular pharyngitis. The Coxackie viruses were recovered from 9 out of 10 throat swabs submitted from these patients and were found in 5 out of the 7 stool specimens examined. By means of the neutralization test, these viruses were typed against the immune sera of six different serologic strains (Types 1, 2, 3, and Group B of Daledorf and Types 4 and 5 of Howitt). They were tested also against the antisera prepared from two of the new strains (D. H. and J. C.). The methods used have been described elsewhere.[5] The results are shown in table 1.

It was found that the four viruses first isolated in 1949, from B. R. and B. P., were all Type 5 (Group A) as previously reported,[5] but that those recovered from the cases of pharyngitis in 1950, belonged either to Type 3 or Type 4 (Group A). In general the latter strains could be grouped according to whether they were neutralized by the antisera or the two new strains (D. H. and J. C.). The former appeared to correspond to the Type 4[5] virus and the latter to the Type 3. One virus (S. S.) was weakly neutralized by the antiserum of J. C. and not by that of the standard types, but was neutralized by the antiserum of B. B. virus. A more detailed study might determine the classification of these two strains.

Serum drawn during the acute phase of the illness showed no neutralizing antibodies in 5 out of 7 patients. Serum obtained from one patient on the fifth day of illness and and another patient on the seventh both showed neutralizing antibodies against their respective viruses. Convalescent serum was obtained from three patients. J. C., whose acute serum failed to neutralize his own virus, was found to have neutralizing antibodies in his serum four weeks later. P. M. C., whose acute serum also did not neutralize her own virus, was found to have neutralizing antibodies seven weeks later. Serum obtained from C. C 10 weeks following onset failed to show neutralizing antibodies.

Discussion

The recovery of the Coxsackie viruses from such a high percentage of patients showing a uniform clinical picture strongly suggests an etiologic relationship. However, Coxsackie viruses have been isolated from patients ill in the summer months with a variety of illnesses. The majority of patients yielding virus were children. The diagnosis in these patients has included nonparalytic and paralytic poliomyelitis, summer grippe, encephalitis, epidemic pleuradynia and fever of unknown origin.

Huebner and his associates[7] at the National Institutes of Health have recently submitted much more critical data on the problem of etiologic relationship of Coxsackie virus to vesicular pharyngitis. These authors encountered the disease in six children in a community of some 300 people which had been under survey for Coxsackie virus. One month prior to the outbreak of the disease in these six patients, the examination of stool specimens collected from 283 persons in the community showed no evidence of Coxsackie virus. In August 1950, the virus was recovered from all six patients with vesicular pharyngitis. High levels of neutralizing antibodies were demonstrated in four of these patients, who

were tested for their presence a few weeks after their illness. During a survey of the community in August 1950, Coxsackie group virus was demonstrated in the stools of 12 contacts, in addition to those of the six patients, but not in the remainder of the persons in the community who had no close contact with the patients.

Conclusions

The Coxsackie group of viruses was recovered from 12 of 13 patients ill with vesicular pharyngitis.

These results strongly suggest a causal relationship between the viral agent recovered and the clinical disease.

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Spanish Abstract

Faringitis Vesicular; Su Relación con el Grupo de Viruses Coxsackie

Durante el verano de 1949 y 1950, se observó un grupo de niños en Jacksonville, Fla., los cuales presentaban el siguiente cuadro clinico: el niño, usualmente menor de cinco años de edad, repentinamente se sintió enfermo con fiebre, malaise y anorexia. El exámen fisico reveló lesiones vesiculares o aftosas en el paladar blando y en los pilares anteriores de la garganta. La fiebre fué de corta duracion, usualmente menos de 48 horas. El cuadro clinico de los pacientes y la aparición de las lesiones en la faringe fué uniformemente constante. Un virus patogeno para el ratón recién nacido fué aislado de las secreciones de la garganta de doce pacientes presentando este cuadro clinico. Este virus resultó ser similar, pero de diferente tipo serológico, al virus previamente descubierto por Daledorf y Sickles y más tarde designado virus Coxsackie. Estos resultados sugieren la existencia de una relación causal entre el virus aislado y la enfermedad clinica descrita.

1569 Palm Avenue

ASPHYXIAL ATTACKS IN THE NEWBORN INFANT DUE TO CONGENITAL OCCLUSION OF THE POSTERIOR NARES

Report of Five Cases

By HARRY MEDOVY, M.D., AND I. H. BECKMAN, M.D.
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CONGENITAL occlusion of the posterior nares (choanae narium) is a rare cause of asphyxial attacks in the newborn infant. When it occurs it constitutes a real emergency. Prompt diagnosis and treatment may be lifesaving.

The anomaly may be unilateral or bilateral, and consists of a bony or membranous partition between the nose and nasopharynx. Nasal breathing is carried on with difficulty in the unilateral cases and is, of course, impossible when the condition is bilateral. The importance of nasal breathing to the newborn infant is not generally appreciated. Thomson[1] states that "With rare exceptions, all infants breathe entirely through the nose. If the nose of a sleeping child is gently closed, he will waken and gasp for breath, instead of simply opening and using the mouth as an airway. Even when mouth breathing is partially adopted to supplement the nasal airway, the latter remains the route preferred by instinct, and as much air as possible is drawn through it. Mouth breathing is an acquired habit."

Bilateral occlusion of the posterior nares may result in severe respiratory distress and even death from asphyxia. Survival is, however, not uncommon, as the case reports will indicate. The literature records 46 cases of untreated bilateral choanal atresia, first recognized between the ages of 20 to 45 years. These cases furnish evidence that the condition is often not diagnosed until failure to obtain relief from adenoidectomy and other nasal procedures has led to the passing of a probe or a catheter into the nares, and to the recognition of the anomaly.

The following cases are reported in order to draw attention to occlusion of the posterior nares as a possible cause of respiratory distress in the newborn period, and to stress the necessity for careful examination of the choanal passages in all cases of neonatal asphyxia.

Case 1. Bilateral Congenital Occlusion of Posterior Nares.—L. H., a full term girl, weighed 2.5 kg. at birth. Within a few hours moderately severe respiratory distress accompanied by blue spells developed. Pharyngeal suction was carried out and when little relief was obtained, suction was performed through an infant laryngoscope. Heart and lungs seemed normal and chest RG was read as negative. Infant continued to have blue spells which were especially severe during attempts at feeding. When a small gavage catheter was passed into the nares, an obstruction was found on both sides about 1.9 cm. from the nasal orifice. An airway was then devised by placing a feeding nipple, with a large opening in it, in one corner of the mouth. The baby then was able to sleep and to feed by dropper without serious respiratory difficulty.

The infant was brought to this Hospital when 9 days of age. There was little respiratory distress with the airway in position, but when this was removed blue spells occurred at frequent intervals. During these spells, there was marked respiratory difficulty with retraction of intercostal and suprasternal spaces. Heart and lungs were normal. Her color was normal between attacks. An attempt to

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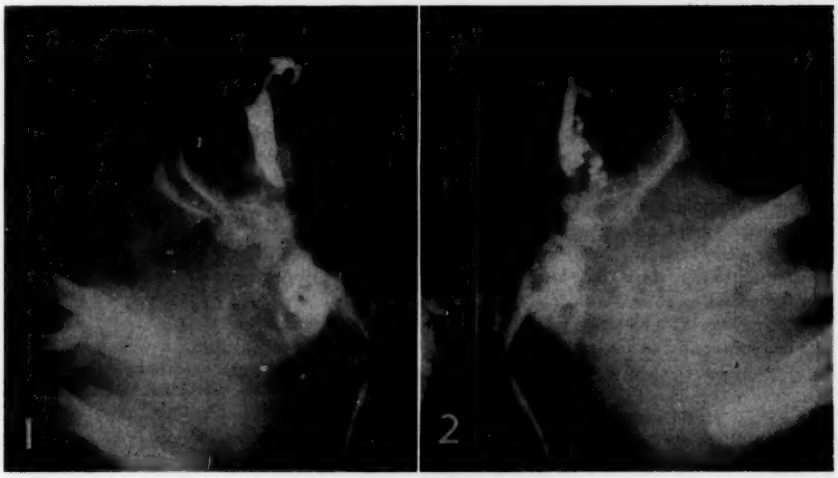
(Received for publication June 15, 1951.)

pass a No. 8F catheter through the nares was unsuccessful. A gavage catheter, passed orally, entered the stomach without difficulty. An attempt to feed by bottle without the airway nipple nearly resulted in a catastrophe. Infant turned blue, then her face became a greyish color, respirations ceased and artificial resuscitation with an airway in the mouth was required to revive.

Roentgen examination was then made by introducing lipiodol, first in one naris, then in the other. The head was tilted back to allow the solution to enter the nasopharynx. No lipiodol appeared in the nasopharynx.

The infant was then taken to the operating room where a steel catheter was gently pushed along the nasal floor until it reached a bony obstruction. A hole was punched through and the opening was enlarged, using a small rasp; a rubber catheter was pushed through and left in place. The procedure was repeated on the opposite side.

No further blue spells occurred. She took feedings slowly without distress, and gained weight.



FIGS. 1 and 2. Case 2 (K. B.). 1. (Left) Lipiodol injected into L naris with infant held on back fails to flow into nasopharynx. Passage is arrested opposite posterior end of hard palate. 2. (Right) Injection of R nostril reveals similar obstruction in posterior part of R side of nose.

On 4th day after operation tubes were removed and a rubber catheter with a steel pilot was inserted twice a week for 6 wk. in order to prevent closure of nasal openings. She was discharged from hospital at 1 mo. of age, weighing 2.6 kg. A month later, because of increasing difficulty in feeding and attacks of respiratory distress, with some retraction of intercostal muscles, she was readmitted for further dilatation of choanal openings. She was discharged 10 days later.

Recent reports are that she is doing well but requires occasional dilatation of choanal openings. Plastic nasal surgery may be required eventually to create permanent nasopharyngeal openings.

Case 2. Bilateral Congenital Occlusion of Posterior Nares.—K. B., a full term girl, weighed 2.6 kg. at birth. She breathed spontaneously, cried well and seemed normal on 1st day. During the next few days she had several cyanotic spells. Heart and lungs were normal. Chest RG showed some evidence of bilateral atelectasis.

The infant was placed on incubator care with continuous oxygen. It was then noted that the cyanotic spells and respiratory distress occurred during nursing or bottle feeding. Submandibular and substernal retraction occurred so that feeding had to be interrupted. A gavage catheter, size No. 8F, passed readily through the mouth into the stomach but when it was introduced into either naris an obstruction was encountered at a distance of about 2 cm. A diagnosis of bilateral congenital choanal atresia was made. Lipiodol plates of the infant's nose, taken with the head resting on the table and the nose pointing directly upwards, were confirmatory (Figs. 1 and 2).

The airway nipple used in Case 1 was also employed in this case, and the mother was cautioned to feed the baby with frequent interruptions so as to avoid any serious respiratory embarrassment.

At 8 wk. of age the infant, now weighing 3.2 kg., was admitted to this hospital, and an attempt made to create at least one nasopharyngeal opening. Bony obstruction was encountered in each choana when a steel catheter was introduced. The patient experienced severe shock, so that the operation had to be ended prematurely. However, it was found possible to pass a size No. 8F catheter through the right naris for several weeks after operation. Both nares continued to fill with gluey, translucent secretion, removal of which made no difference to the infant's breathing. Feeding was a long and arduous process. She would suck, become breathless, push the nipple from the mouth, take a few vigorous inspirations, and then search for the nipple and resume feeding.

Infant slept with thumb in her mouth after 3rd month, and this evidently served to create a satisfactory airway for when, as occasionally happened, the thumb would slip out of her mouth during sleep, she would waken suddenly, gasp for breath, re-insert her thumb and fall quickly into a quiet sleep. When the infant was held upright, a large quantity of mucus flowed slowly out of both nares. Mother noted that, occasionally, mucus in R naris would move up and down, suggesting that a tiny opening, created at operation, still remained.

The infant is now 2 yr. of age and weighs 11.8 kg. She walks and talks, and looks very well. There is no difficulty in feeding or breathing. Both nasal passages are filled with a mucoid, odorless secretion, but on R side occasional bubbling occurs, indicating a tiny airway has persisted.

Case 3. Unilateral Congenital Occlusion of Posterior Nares.—S. M., male. Delivery and resuscitation were uneventful. Examination on day after birth revealed normal findings and course was uneventful throughout entire nursery stay.

When he was 12 days old mother reported that he had developed a "head cold." She noticed that discharge seemed to come from one nostril only. When infant was 16 days old, mother reported that in addition to her worry about the "cold in one nostril" she was even more concerned by the fact that he seemed to go into a "faint" while feeding. Examination showed no unusual findings except for the presence of a large amount of gluey, odorless, translucent secretion in R nostril. Diagnosis was not suspected, but in view of mother's concern, the infant was readmitted to Winnipeg General Hospital for observation. An attempt was made to pass a probe into the nares when it was found that there was a complete bony occlusion of R nasal choana. Probe passed readily through L nares into the nasopharynx. Chest RG was negative. A diagnosis of unilateral choanal atresia was made. It was decided to defer operative procedures in view of patency of L nasal passage. The infant has progressed normally but still has a collection of mucus in R nares.

Case 4. Bilateral Congenital Occlusion of Posterior Nares*.—H. J., male infant. Delivery was uneventful but resuscitation was difficult and the infant continued to have difficulty in breathing. Color was mildly cyanotic and there was periodic inspiratory indrawing of infra- and suprasternal spaces. Respiration was particularly difficult during attempts at feeding and severe asphyxial attacks occurred. On 3rd day, an attempt to pass a No. 8F nasal catheter into nasopharynx was unsuccessful on both sides. Lipiodol films taken with nose pointing upwards were confirmatory of bilateral occlusion of the nasal choanae.

The infant was fed slowly and feeding was interrupted frequently to allow for difficulty in breathing. He gained weight slowly but managed to maintain good nutrition. At 5½ mo. of age, both bony nasal plates were perforated with burrs, the openings enlarged with back-cutting forceps, and 2 tantalum tubes inserted and held in place with sutures brought forward to anterior septal margin. Breathing became normal and has remained so ever since. One month after operation, tubes were removed. Infant is now 15 mo. old, and is well nourished and normal.

Case 5. Unilateral Occlusion of Posterior Nares Associated with Congenital Heart Disease.—D. N., a white male, weight 2.7 kg. Delivery was normal but resuscitation was accomplished with great difficulty and color was never satisfactory during nursery stay. Feeding was a difficult procedure. Infant seemed tired and short of breath and would push nipple out of his mouth frequently. There were no severe asphyxial attacks. At age of 5 wk. he was cyanosed, short of breath and unable to feed. On examination, he was poorly nourished, with a moderately pronounced inspiratory stridor. Heart was enlarged, and a blowing systolic murmur was heard at sternal margin in 3rd L ICS. Liver

* Case of Dr. Murray McLandress and Dr. E. J. Washington.

edge could be felt 4 cm. below R coastal margin. Coarse rales could be heard throughout both lungs.

Femoral pulse was noted on both sides. A diagnosis was made of congenital heart disease with cardiac failure, and infant was hospitalized and treated with oxygen and digitalis. Improvement was rapid, and in a few days both liver and heart had returned to normal size. Respiratory distress continued, however, and occasional blue spells were reported during feeding. It was impossible to pass a No. 8F catheter through R nasal space. Roentgenographic study with lipiodol in R nasal space confirmed the diagnosis of congenital occlusion of R posterior nares.

The infant was given careful, interrupted feedings and his nutritional status remained good. Attempts were made to pass a catheter on the obstructed side and on the third occasion it was found possible to ease the catheter into the postnasal space. Lipiodol plates were repeated and this time the lipiodol appeared in the pharynx immediately after it was introduced. It would appear that the obstruction in this case was not bony in origin and that it was relieved by the repeated attempts to pass the catheter.

Discussion

Frequency of Occurrence: Fewer than 300 cases of congenital occlusion of the posterior nares are recorded in the literature up to 1945. Of these, 115 were bilateral. The first case was described by Emert in 1863. It was a bilateral obstruction. Only six cases, all unilateral, were reported in a 20 year period by Turner. Twelve cases were reported from the Mayo Clinic in the period 1907-1939. Ten cases are reported from the Massachusetts Eye and Ear Infirmary, among a series of 62,228 patients.

No report on the occurrence of this condition among newborn infants has been made. It is probable that the incidence is greater than is reported.

Diagnosis

The diagnosis can be made with ease once the condition is suspected. Where the obstruction is bilateral, there is serious interference with respiration during feeding. At this time, the apposition of tongue and palate combine with the nasal obstruction to make breathing impossible. As a result, asphyxial attacks occur with marked retraction in the infrasternal and submandibular regions. In some cases respiratory distress may occur even when the baby is not feeding. The condition is much more serious in the first few weeks of life, because of the dependence of the newborn infant on nasal breathing. As mouth breathing develops, and the infant is able to feed by means other than sucking, the danger of asphyxia becomes less.

Thus, intermittent cyanosis with evidence of respiratory obstruction during feeding should lead at once to careful examination of the nares. The diagnosis can readily be made by the inability to pass a small nasal gavage catheter through the nares into the pharynx. The diagnosis may then be confirmed by roentgenographic films made when lipiodol is dropped into one nasal space and then the other, with the infant's head tilted back (Fig. 1). Finally, a probe may be used to determine whether the obstruction is membranous or bony.

The unilateral choanal obstruction is suspected less frequently since the respiratory distress is not severe. Asphyxial attacks, if they occur at all, are minimal and transitory, so that reliance must be placed on the occurrence of unilateral nasal discharge of a characteristically glairy, translucent type. In some instances stenosis rather than atresia may be encountered. The infant who breathes noisily during feeding, and who is often referred to as a "snorter," will be found to have narrow choanal passages, so that one will have considerable difficulty in easing a No. 8F gavage catheter through the nares. In some instances, it will be found impossible to pass the gavage catheter, but roentgenographic

examination with lipiodol in the nares and the head tilted back will demonstrate that the nares are patent, but stenotic. These cases improve rapidly with the growth of the infant and present no serious problem.

It is important, also, for the pathologist to keep this condition in mind when doing an autopsy on an infant dead of asphyxia. It is quite possible that in many instances the examination of the nares is overlooked in death, as it is in life, and that some infant deaths which have been attributed to enlarged thymus, or to incipient pneumonia not too clearly demonstrated, may, in fact, have been due to asphyxia resulting from an occluded nasal airway.

Management

Once the diagnosis is made, treatment depends on the type of malformation and the severity of the symptoms. In the unilateral cases there is rarely serious respiratory difficulty, and surgery may be postponed until later childhood. Feedings should, nevertheless, be given with care and with frequent interruptions to allow for satisfactory breathing.

Where the obstruction is bilateral, respiratory symptoms may be severe and may occur between feedings as well as during feedings (Cases 1 and 4). In these cases two problems have to be faced; the difficulty of maintaining adequate nutrition with slow, interrupted feedings and the danger of death during an asphyxial attack. The use of an artificial airway as in Case 1 makes feeding less precarious and may be lifesaving. In any event, feeding will be difficult, and the infant's progress will be slow. In Case 1, symptoms were so severe that artificial openings were made at the age of 6 days and maintained by frequent dilatations. In Case 4, artificial nasal openings were made at 5½ months of age, and were followed by dramatic improvement in the infant's breathing and subsequent rapid gain in weight. In Case 2, careful feeding and extraordinary care on the part of the mother made it possible to defer operation until the infant was 8 weeks old, at which time a small opening was made on one side. This gave partial relief to the infant and made feeding less hazardous. The use of the thumb by this infant to maintain a good airway during sleep is noteworthy.

Summary

Asphyxial attacks in newborn infants may occasionally be due to congenital occlusion of the posterior nares. The diagnosis may be made by observation of the infant during feeding, by inability to pass a catheter or probe through the nares into the nasopharynx and by roentgenographic studies with lipiodol in the nasal passages.

Treatment is surgical and may be carried out successfully in early infancy if the condition is bilateral. Treatment of the unilateral cases may be deferred to later childhood. Autopsy on a case of sudden asphyxial death in an infant should not be considered complete until the nasal openings are examined.

Acknowledgment

The authors acknowledge assistance from Prof. Bruce Chown, Department of Pediatrics, Asst. Prof. I. W. Monie, Department of Anatomy, University of Manitoba, and Dr. A. E. Childe of the Department of Radiology, Children's Hospital, Winnipeg.

Appreciation is due Dr. Murray McLandress and Dr. E. J. Washington for the opportunity of seeing Case 4 and for permission to publish it.

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SPANISH ABSTRACT

Ataques de Asfixia en Recién Nacidos Debidos a la Oclusión Congénita de las Coanas Posteriores de la Nariz

La oclusión congénita de las coanas (nares) posteriores de la nariz se encuentra entre las causas poco comunes de trastornos respiratorios agudos. Esta malformación puede ser unilateral o bilateral y la obstrucción puede ser de tipo membranosa o de tipo óseo, o una combinación de ambos. Debido a su rareza esta malformación es frecuentemente olvidada. El diagnóstico puede hacerse facilmente siempre que la posibilidad de ocurrencia se tenga presente. La imposibilidad en pasar un cateter numero 8F. atráves de las coanas dentro de la nasofaringe, y la confirmación radiológica mediante la instilación de lipiodol en las coanas son indicativos de la presencia de una obstrucción coanal. Los casos con obstrucción unilateral pueden ser tratados mas tarde en la niñez, pero los casos de obstrucción bilateral deben ser operados inmediatamente y aberturas artificiales deben crearse. Se reportan cinco casos, de los cuales tres presentaban una obstrucción bilateral.

The University of Manitoba

SEXUAL PRECOCITY IN FEMALES

Report of Two Cases, With Arrest of Precocity in the McCune-Albright Syndrome After Removal of a Cystic Ovary

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THERE are approximately 645 case reports of sexual precocity in the medical literature,[1] of which 449 are in females. Of these, 310 are of the so-called constitutional type, 68 of cerebral origin, and 71 due to ovarian tumors. Twenty-eight of the 68 cases classified as of cerebral origin are cases of polyostotic fibrous dysplasia (McCune-Albright syndrome). Virilizing adrenal tumors occur occasionally in females but are not within the scope of this paper.

Two cases are reported here, one of the McCune-Albright syndrome, and one of constitutional precocity. It is felt that the case of the child with McCune-Albright syndrome is of particular interest, as removal of a cystic ovary has arrested the symptoms and signs of sexual precocity. No other cases of this syndrome have been reported with similar ovarian findings and response to therapy. The only case found in the literature at all similar is one reported by Kimmel,[2] in which a two year old child with sexual precocity lost all precocious signs after removal of an ovary containing a large follicular cyst; that child did not have the McCune-Albright syndrome; the author considered her precocity a direct result of a primary follicular cyst.

REPORT OF CASES

Case 1. B. R. S., aged 5½ yr., was first seen by her physician because of vaginal bleeding which had first appeared at 3 yr. of age of a spotting type off and on; for 1 wk. prior to admission she had bled steadily from the vagina. Her mother and father were in good health, one sibling was living and well, and another had died from prematurity.

On examination she was large for her age and showed adolescent breast and genital development (Figs. 1 and 2). Sparse pubic hair was present on the mons veneris as well as in the axillae. Temperature was 37.2°C. Weight was 24.5 kg., height 120 cm. She was alert and seemed bright for her age. There was slight prominence of L side of the forehead present since early infancy which was considered to be within normal limits. Three café-au-lait spots were present on the back and had been there since birth (Fig. 3). They had grown only with body growth. Normal blood count and urinalysis. RG of sella turcica was mistakenly reported as normal and examination of wrists revealed a bone age of 10 yr. (Fig. 4). Chest RG was negative. Rectal examination was negative. Intravenous pyelogram was normal. No urinary bioassays were made then. Vaginal smear showed cornified epithelium.

Diagnosis of McCune-Albright syndrome was not made at the time, and exploratory laparotomy was advised and carried out. Adrenal regions were normal. Right tube and ovary were normal in size and position. Left ovary was several times enlarged and showed bluish discoloration (Fig. 5). It appeared somewhat cystic. Uterus was slightly enlarged. Appendix was enlarged and injected. Left ovary and appendix were removed and the wound closed. Ovarian sections were reported as containing 2 large luteinized follicular cysts and numerous primordial follicles. Evidence of granulosa cell tumor was not found.

Patient made an uneventful recovery from surgery and went home in good condition. After

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(Received for publication May 15, 1951.)

receiving the report of microscopic examination of the ovary, the parents were advised that further observation of the child would be necessary to rule out some other underlying cause for her sexual precocity. Two 24 hr. urine samples* showed no estrogenic activity in either sample; if any were being excreted it was less than 5 international units/24 hr. 17-ketosteroid assays also gave low values.

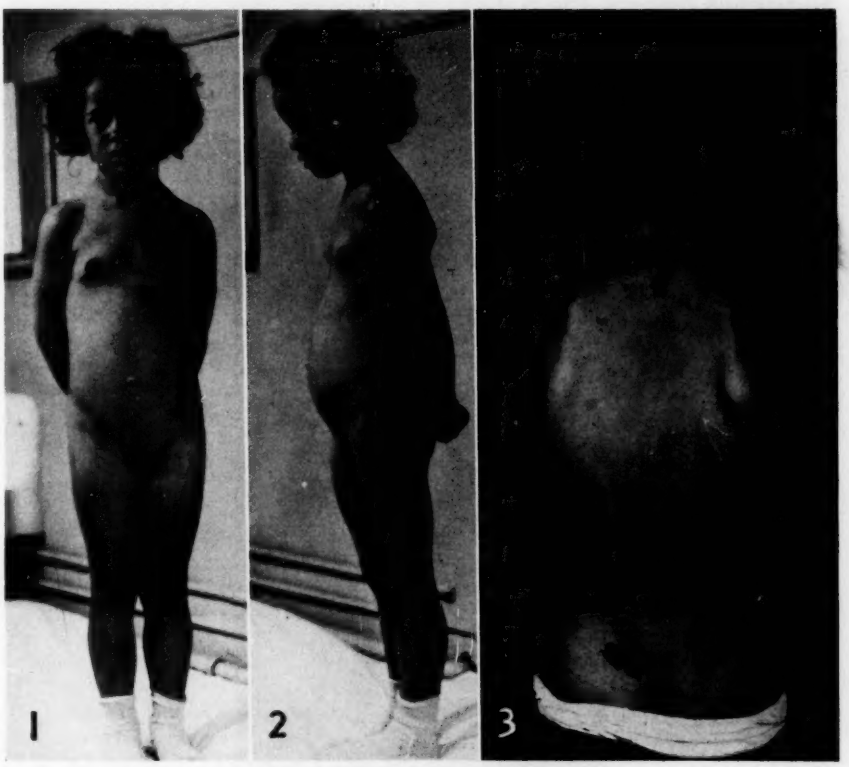

Fig. 1. (Case 1, B. R. S.) McCune-Albright syndrome. Pubic hair and adolescent breast development are present.

Fig. 2. (Case 1) Side view outlining adolescent body contours.

Fig. 3. (Case 1) Posterior view showing café au lait spots on back, chiefly on left side except for top-most one which is just to right of midline.

Sample #1 contained 0.8 mg. and sample #2 contained 0.6 mg., normal for a 5 yr. old girl. No urinary gonadotropin studies were carried out.

Following surgery, secondary sex characteristics began to subside and there was no further menstrual bleeding. She was seen on several occasions during the following year and her progress was entirely favorable. A year and a half later the child had slight vaginal spotting for 2 days. On examination she showed regression of breast and labial development, although labia were still somewhat larger than normal for age and there was still a sparse amount of pubic hair. Temperature was normal. Weight was 29.0 kg., height 129 cm., which was a large growth and gain as compared to 1½ yr. before. Blood pressure was 92/58 mm./Hg. General physical findings were similar to those obtained originally except that L side of face and forehead seemed to be more prominent and she was com-

* Sent to Dr. Leo Samuels, University of Utah.

plaining of headache. Examination of eye grounds and refraction showed fundi were normal, right eye 20/20 vision and left eye 20/200. Roentgenographic examination of skull and entire skeleton showed significant changes consisting of markedly dense structure of entire L sphenoid bone together with a filling density of L orbit and obliteration of paranasal sinuses. Left frontal bone also was more dense than normal (Fig. 6). There were unilateral bone changes in L humerus, radius and

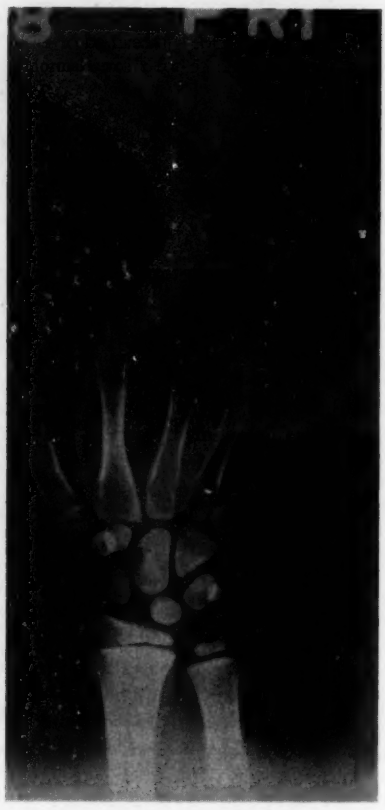

Fig. 4. (Case 1) Carpal centers showing bone age of approximately 10 yr. as compared to chronologic age of 5½ yr.

ulna which were reported to be compatible with fibrous dysplasia (Fig. 7). These unilateral bone changes, with café-au-lait spots on the same side, and sexual precocity, finally led to a diagnosis of McCune-Albright syndrome (polyostotic fibrous dysplasia). Serum Ca was 9.3 mg., phosphorus 3.2 mg., alkaline phosphatase 3.0 Bodansky units/100 cc. Urinalysis was negative and other laboratory findings which were repeated were also normal.

She has been in good general health up to the present time, and has had no more vaginal bleeding. There have been no symptoms related to the bones except for some pain in the left eye. The vision has not changed. Further roentgenographic studies have not been made. Last complete examination was at the age of 8 yr., 10½ mo. Weight at that time was 30.8 kg., height 135 cm., as compared to an average weight of 25.9 kg. and height of 116 cm. External genitalia, hair growth, and breast development had not changed during the previous 2 yr. Patient seemed intelligent for age and was doing well in school.

A female sibling was born subsequently who showed no evidence of the McCune-Albright syndrome or other abnormalities.

Case 2. P. S., 4½ yr. of age, was born weighing 2.9 kg., in good general condition. Mother, father and one sibling were in good health. She weighed 4.5 kg. at 6 wk. of age, and 14.5 kg. at 14 mo. She was seen at 3 yr. of age because of vaginal bleeding occurring at monthly intervals for the previous 4 mo., lasting for about 4 days each time. There were no other complaints except that she was wearing a Ponsetti abduction bar for correction of a dislocated left hip which had been under treatment since 2 yr. of age. Parents said that her appetite was large. She was large for a 3 yr. old

Fig. 5. (Case 1) Ovary and appendix. Ovary is more than twice as large as normal and of cystic consistency. It shows bluish discoloration.

(Figs. 8 and 9), with a weight of 26.1 kg. and height of 99 cm. Vulva showed adolescent development. Sparse pubic hair was present but no axillary hair. Breasts showed adolescent development; this could be felt better than seen because of the general obesity of the child. Pigmented spots could not be seen on the skin. Her physician had made a rectal examination under anesthesia and had found no masses in the pelvic region. Roentgenographic examination of skull and complete skeleton showed no abnormalities compatible with polyostotic fibrous dysplasia; bone age was approximately 10 yr. (Fig. 10). Blood count: Hgb. 13 gm./100 cc., RBC 4 million/cmm., leukocytes 7.5 thousand/cmm. with lymphocytes 57%, monocytes 2%, segmented cells 30%, eosinophils 10% and basophils 1%. There were a few atypical lymphocytes. Urine showed sp.g. 1.022, pH 6.0, negative albumin and sugar. Serum Ca was 10.8 mg./100 cc., phosphorus 4.77, alkaline phosphatase 7.6 Bodansky units.

Urinary bioassays were carried showing gonadotropins between 6 and 12 mouse units/24 hr., an increased amount for a child but normal for an adult. Estrogen titer was approximately 30 mouse units/24 hr.; this also represents an elevation for a child and a normal value for an adult. Assay of 17-ketosteroids excretion totalled 1.5 mg. in 24 hr., an elevated value for a child but somewhat low for an adult.

These findings all pointed to a diagnosis of sexual precocity of constitutional type. However, because of the possibility of ovarian changes similar to those in Case 1, exploratory laparotomy was recommended. She was admitted to St. Luke's Hospital and surgical exploration was made; uterus, tubes and ovaries had the development of early adolescence. No masses in the genital or adrenal regions were noted. The appendix contained several fecoliths and was removed. It was thought that these findings confirmed the diagnosis of constitutional type of sexual precocity. The parents were

advised of the probable long-term favorable outlook with eventual moderate stunting of growth as the only residual effect of the precocity.

The most recent examination of the child 1 yr. later at the age of 4 yr., 4 mo., showed weight 33.4 kg., height 124 cm., as compared to average values of 15.4 kg. and 100 cm. at 4 yr. of age.

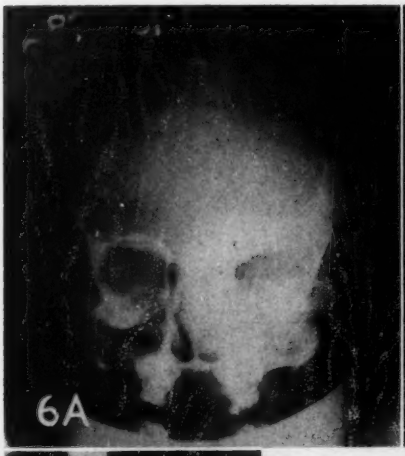

Fig. 6. (Case 1) A. AP skull RG showing increased density and sclerotic overgrowth of left facial, orbital and frontal bones. B. Left lateral view of skull showing sclerotic increase of density at base of skull.

Fig. 7. (Case 1) Fibrous dysplasia of left radius, ulna and humerus.

Mother reported vaginal bleeding for 2 days in January 1950 (operation in March 1950), slight bleeding for one day in September and December 1950, and profuse bleeding for 2 days in February 1951. Vulva appeared more mature, with more pubic hair than before. Axillary hair was not present. Breasts were more enlarged. Two lower central permanent incisor teeth had appeared; teeth were all in good condition. She was without the abduction bar and walked without a limp.

Discussion

Adolescent sexual changes may begin normally in girls as young as 8 years of age. The onset of such changes before this age is considered precocious. If there is a true ovulatory cycle, even though irregular, most authors prefer to call this precocious puberty[3, 4]

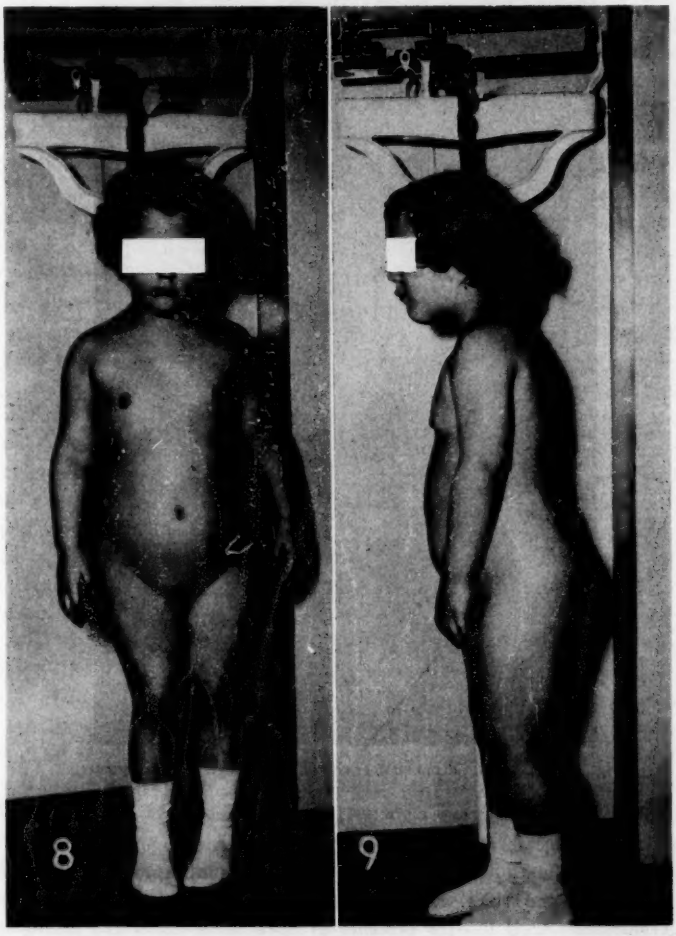

Fig. 8. (Case 2, P. S.) Patient with constitutional precocity, showing large body build. Breast hypertrophy is somewhat disguised by general obesity. Pubic hair is present to sparse degree.

Fig. 9. (Case 2) Lateral view showing precocious development and growth of 3 yr. old child.

rather than sexual precocity. If one accepts this terminology, both of the cases reported here would be considered cases of precocious puberty. Primary ovarian tumors, such as a granulosa cell tumor, would then cause sexual precocity but not true precocious puberty.

In diagnosis of a case of sexual precocity or precocious puberty, the special points of

importance in the examination include degree and type of changes in secondary sex characteristics, careful rectal examination to rule out ovarian tumor, the presence or absence of spots of skin pigmentation, and the size of the child compared to normal range for age. A vaginal smear should be made for cornified squamous epithelial cells, the presence of

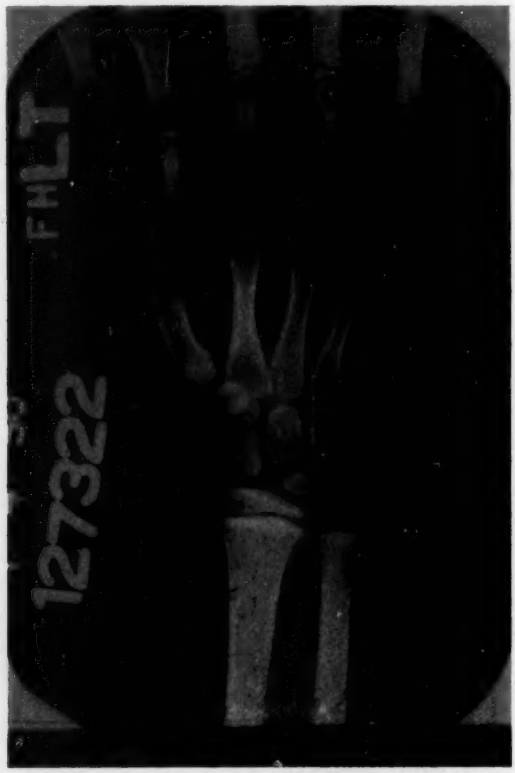

Fig. 10. (Case 2) Carpal centers showing bone age of approximately 10 yr. in 3 yr. old child.

which indicates estrogenic activity. If any masculinizing changes are present, there is increased hair formation, a masculine type of body build, enlargement of the clitoris, and possibly changes in the voice. Roentgenographic studies include growth centers for osseous development, skull RG for evidence of intracranial tumor and fibrous dysplasia of bone, and complete skeletal RGs to detect fibrous dysplasia. If any masculinizing changes are present, an intravenous pyelogram is indicated. Urinary bioassays are carried out on 24 hour samples and include determination of pituitary gonadotropins, estrogens and 17-ketosteroids. In childhood, excretion of gonadotropins (F.S.H.) is less than six mouse units/24 hr.; in adults there is a normal range of 6 to 52 units/24 hr. Urinary estrogen amounts to 0 to 10 mouse units/24 hr. in girls under 8 years of age, and 0 to 1000 units in women. Excretion of 17-ketosteroids is less than 1 mg./24 hr. in childhood,

and 5 to 14 mg. in adult life. Serum calcium, phosphorus and alkaline phosphatase determinations are indicated in cases with bone involvement. Endometrial biopsy just before a menstrual period can be done to decide whether a cycle is ovulatory. Exploratory laparotomy is required in some cases in which the etiology remains in doubt.

The McCune-Albright syndrome, of which Case 1 is an example, consists of polyostotic fibrous dysplasia, spots of brown skin pigmentation, and sexual precocity in females. The skin changes and bone involvement are usually unilateral, both confined to the same side of the body. Skin pigmentation is not always present. In males this syndrome is not associated with sexual precocity. This disease was described first by McCune and Bruch[5] and by Albright.[6] The etiology is not definitely established but it is probably the result of congenital defects in the hypothalamus, osseous system and skin. The sexual precocity arises from pituitary stimulation of the gonads and results in true precocious puberty. In Case 1 it is presumed that removal of the cystic ovary did not change the underlying cause of the sexual precocity, but simply removed an extremely sensitive end-organ; no explanation is offered as to why this ovary reacted in a more sensitive manner than the other one. The child's precocity with respect to body growth and osseous development continued unabated after removal of the cystic ovary. The bone changes in the McCune-Albright syndrome consist in the extremities of areas of rarefaction as a result of fibrous dysplasia, sometimes severe enough to cause fractures, but usually not progressive. In the skull, the bone changes consist of sclerotic overgrowth of the base of the skull, sometimes involving the orbit and facial bones with resultant asymmetry, proptosis and loss of vision. Bone age and body growth are advanced during childhood, but there is eventual stunting of growth due to early closure of epiphyses. Calcium and phosphorus metabolism is normal, but serum alkaline phosphatase values are often elevated. Urinary bioassays should yield moderate elevations of gonadotropins, estrogens and 17-ketosteroids such as one would expect in a normal adolescent child. The prognosis is favorable in cases in which the bone changes are not progressive. A normal reproductive span during adult life can be anticipated in uncomplicated cases.

About 90% of all cases of sexual precocity are of the constitutional type, if all cases were reported.[1] P. S. (Case 2), is of this type. In these cases, a normal type of puberty occurs at a younger-than-normal age. The etiology is not known. As in the McCune-Albright syndrome there is advanced body growth and bone age with eventual stunting of growth. The prognosis is good. In diagnosis one must especially consider neurogenic causes such as intracranial tumor, encephalitis, cerebral defect, and in males pineal tumor. Ovarian tumors such as granulosa cell tumor, teratoma and chorionepithelioma must also be ruled out. In them a palpable pelvic mass may be present. Urinary estrogen excretion is much higher in these cases than in constitutional precocity or in the McCune-Albright syndrome. There is no increase in gonadotropins such as one sees in constitutional cases. Granulosa cell ovarian tumor has been identified as a cause of sexual precocity in 31 cases. It is potentially malignant and should be removed surgically as soon as possible. Chorionepithelioma has been found in six cases, and teratoma in four cases; chorionepithelioma is especially malignant; both should be removed surgically as soon as possible.

Summary

Two cases of sexual precocity in female children are reported. One child with the McCune-Albright syndrome had her onset of menses at 3 years of age. Surgical removal

of an ovary containing luteinized follicular cysts and primordial follicles has resulted in arrest of her sexual precocity over a period of almost four years, giving her a more normal childhood than would otherwise have been possible.

The other child has findings diagnostic of the constitutional type of precocity, by far the most common type. Vaginal bleeding in her case began at 4 years of age. In view of the favorable effect of finding and removing a cystic ovary in the child with McCune-Albright disease, this child was explored surgically. There were early adolescent changes in the uterus, tubes and ovaries, but no other abnormalities were found.

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Spanish Abstract

Precocidad Sexual en Niñas; Reporte de Dos Casos

El autor reporta dos casos de precocidad sexual ocurrida en dos niñas. Una niña presentaba el sindrome de McCune-Albright, consistente en una displasia poliostotica fibrosa unilateral, manchas "cafe au lait" de la piel y precocidad sexual. El comienzo de la menstruación ocurrió a los tres años de edad. La extirpación de un ovario conteniendo quistes luteinizados foliculares y tambien folículos primordiales a la edad de cinco y medio años, resultó en el arresto de la precocidad sexual, aunque no afectó a la precocidad de crecimiento del cuerpo, ni tampoco afectó la maduracion ósea. El otro caso consistió de una niña presentando una precocidad sexual de tipo constitucional, la cual es de ocurrencia mucho más común. En este paciente la menstruación comenzó a los cuatro años de edad. El desarrollo del cuerpo estaba aumentado en relación con la edad y la edad ósea tambien estaba avanzada. Las gonadotropinas, estrogenos y 17-ketoesteroides de la orina revelaron concentraciones de niñas adolescentes. Una exploración quirúrgica fué esencialmente negativa a excepción de la apariencia adolescente del utero, trompas y ovarios. El pronóstico en este caso parece ser bueno con una futura vida reproductiva normal; el único efecto residual será un retraso (stunting) del crecimiento. El pronóstico del caso presentando el síndrome de McCune-Albright es también favorable debido a que la displasia fibrosa de los huesos no parece ser de caracter progresivo al momento presente; aunque aquí tambien ocurrirá eventualmente un retraso del crecimiento.

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EPIPHYSEAL INJURIES IN BREECH DELIVERY

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DURING the course of a breech extraction or breech presentation with version and extraction, injury to the extremities may be a complication. Trauma and separation of an epiphysis, with or without apparent dislocation may occur. When this involves the upper or lower femoral epiphysis, a sequence of changes takes place which forms a characteristic clinical and pathologic picture. There is usually no hint of injury until the second day of life when the infant assumes the "frog" position, with the affected extremity held flexed at the knee and hip and externally rotated. The soft tissue over the involved area is full, tense and often reddened. There is marked tenderness and pain on passive motion. The patient is extremely irritable and may have a low grade fever. Roentgenograms, which are negative for about the first five days, begin to show subperiosteal changes indicating local calcification of extravasated blood at the site of the injury.

A similar picture prevails when the injury involves the upper extremity. The injury usually involves the upper humeral epiphysis and there is overlying soft tissue swelling with alteration of the normal shoulder contour. In this instance the affected limb is held limp, extended and externally rotated. There is pain on motion. Roentgenographic changes follow the same pattern as those for the lower extremities.

Kennedy[1] reviewed 20 cases of traumatic separation of the upper femoral epiphysis and added one case of his own. Snedecor, Knapp and Wilson[2] had previously reported two cases of "Traumatic Ossifying Periostitis" which were included in Kennedy's series of upper femoral epiphyseal injury due to birth trauma. Such injuries are not limited to the femora. Snedecor and Wilson[3] described 11 cases of obstetric injuries to the long bones. Of these, one affected the upper humeral epiphysis, seven involved the femur alone, and in three cases, both the femur and tibia were involved. Where there were multiple periostotic reactions, the involvement was always on the same side. Scagliatti[4] reported 53 cases involving the upper end of the humerus.

This paper reports four cases of epiphyseal injury and subperiosteal hemorrhage due to birth trauma. All cases reported occurred as direct or altered breech extraction.

Case 1: B. H., a 3000 gm. female infant, was born of a healthy primiparous mother after an uneventful full term gestation. The presenting breech was decomposed by the Pinard technic and delivered apparently without difficulty after 8 hr. of labor. There was spontaneous breathing and no anomalies were present.

The R lower thigh was swollen and ecchymotic, and there was swelling of R knee on the day after delivery. Right leg was held semi-flexed and externally rotated. Motion was completely limited on the affected side by 3rd day. RG at this time was reported as negative for injury. By 7th day RGs revealed small calcific spicules at the lower end of R femur. Films were not made again until 3rd wk. of life, at which time there was evidence of extensive subperiosteal calcification at lower end of R femur (Fig. 1). At this examination, swelling and limitation of motion had completely disappeared. However, there was palpable anterior bowing of femur which appeared on the serial films taken during the next 12 mo. (Fig. 2). At 3 yr. of age, there is no bowing or limp.

Case 2: B.R., Negro female infant weighing 4850 gm., was born at term of a multiparous mother

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(Received for publication April 25, 1951.)

after an uneventful full term gestation. The presenting part was the breech, and delivery was accomplished by decomposing a frank breech to a footling, and applying traction to the legs. Infant cried spontaneously and no anomalies were noted. There was slight edema of both lower extremities, and a small 3 mm. laceration of the posterior fourchette. Thirty-six hours after delivery, infant's L lower extremity was noted to be edematous from thigh to ankle. There was no abnormal mobility or crepitation, but the affected part was exquisitely tender on passive motion, and was held flexed at hip and knee. There was no increased heat and no discoloration over the injured limb.

FIG. 1. Case 1, 3rd wk. of life. Subperiosteal calcification at R lower femoral epiphysis.
FIG. 2. Case 1, 5 mo. of age. Complete disappearance of subperiosteal calcification. Marked anterior-posterior bowing.

Two days after birth a purulent discharge developed at the laceration of the fourchette and the temperature rose to 37.8°C. WBC count was 11.2 thousand/cmm., 70% leukocytes, 28% lymphocytes and 2% mononuclear cells. A blood culture was sterile.

Infant was started on intramuscular penicillin therapeutically, and vitamin K prophylactically.

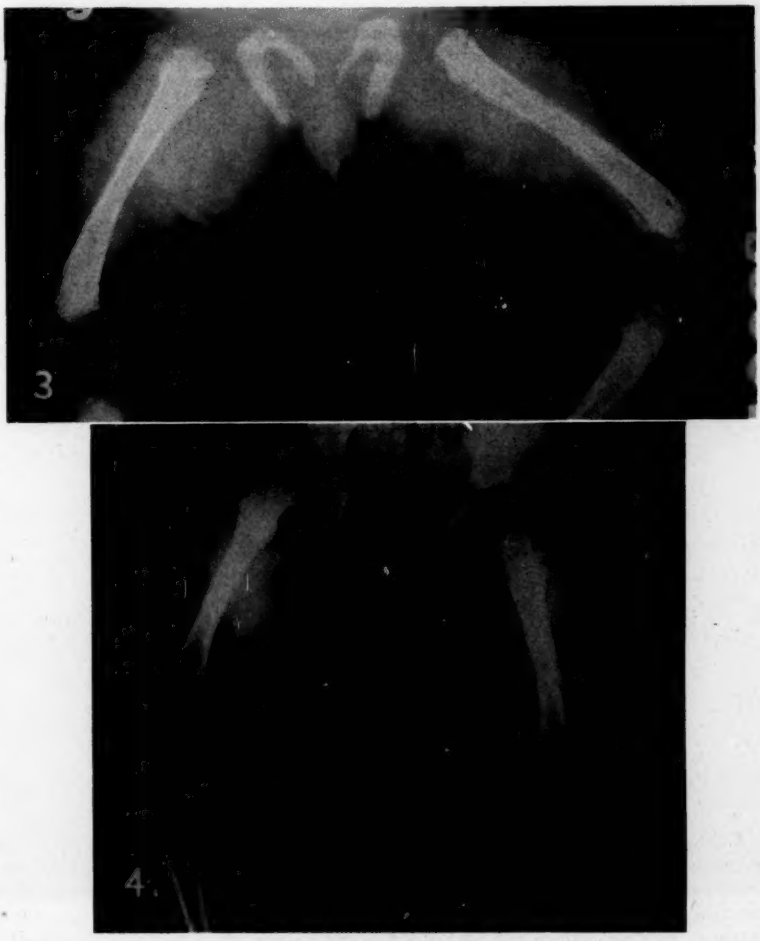

FIG. 3. Case 2, 9 days of age. Deposition of subperiosteal calcification at L lower femur.
FIG. 4. Case 2, 5 wk. of age. Early healing with thickening of cortex at L lower femur, with moderate widening of L lower metaphysis.

On 3rd day of life RG of the lower extremities showed only soft tissue swelling. During the 3rd to 6th day of life, temperature was normal and swelling and tenderness of the left thigh decreased. Left leg continued to be held in a position of flexion and external rotation. The wound of the fourchette healed completely.

On 9th day, RG showed subperiosteal calcification at the distal end of the femur on the left (Fig. 3). At this time there was no limitation of motion and infant appeared greatly improved. By

the 13th day all clinical signs of injury were gone. Further RGs showed a considerable increase in the subperiosteal callous formation (Fig. 4).

Case 3: S. S. was born at term of a primiparous mother after an uneventful pregnancy. Infant was delivered spontaneously as a single footling breech extraction. Attending physician encountered no difficulty after performing an episiotomy. Weight was 3800 gm.

On day following birth it was noticed that L upper extremity was held in full outward rotation and extension when left unsupported, and remained limp and motionless. There was an anterior bulge of L shoulder due to soft tissue swelling, causing loss of normal shoulder contour. RG taken at this time was reported as negative for fracture or dislocation. On 3rd day of life infant began to move the L arm, and at discharge on the 6th day was moving arm actively.

At 5 wk. of age infant was readmitted to hospital because of persistent deformity of L shoulder.

FIG. 5. Case 3, 5 wk. of age. Marked subperiosteal calcification at L upper humeral epiphysis.

There had been no limitation of motion or pain. RGs taken on this admission revealed marked subperiosteal calcification, particularly about lateral aspect of L upper humerus (Fig. 5). Upper portion of the normally ossified humerus appeared at a lower level than first seen on the initial film, and indicated a minimal displacement of the upper humeral epiphysis.

Because of excellent position and normal growth and function, no therapy was advised. At 2½ yr. of age, patient continues to have freedom of motion and no alteration in growth. No further RGs were obtained.

Case 4: R. C. a 10 day old male infant was admitted to hospital for examination. He was born at term at another hospital of a primiparous mother. He was delivered by an apparently uncomplicated breech extraction. Parents were informed that during the nursery stay infant maintained an "abnormal position of the legs," as well as fever. RGs taken on the 3rd day were reported as negative. Infant was discharged on the 9th day of life, at which time the baby cried each time legs were moved or handled. On day after discharge infant had several loose stools, and because of the diarrhea and painful legs, was admitted to the hospital.

On admission temperature was 37.2°C. Infant appeared uncomfortable, and preferred to maintain

lower extremities in marked external rotation, in "frog" position. There was considerable swelling of the lower third of both thighs, and he cried whenever legs were touched.

On day of admission, blood showed RBC count 4.5 million/cmm., Hgb. 16 gm./100 cc., WBC count 27.0 thousand/cmm., with leukocytes 66% and lymphocytes 34%. Urine analysis was negative.

RGs of long bones taken on admission revealed osteochondritis of lower third of both femora, with slight periosteal reaction in these areas (Fig. 6). Five days later, re-examination showed definite

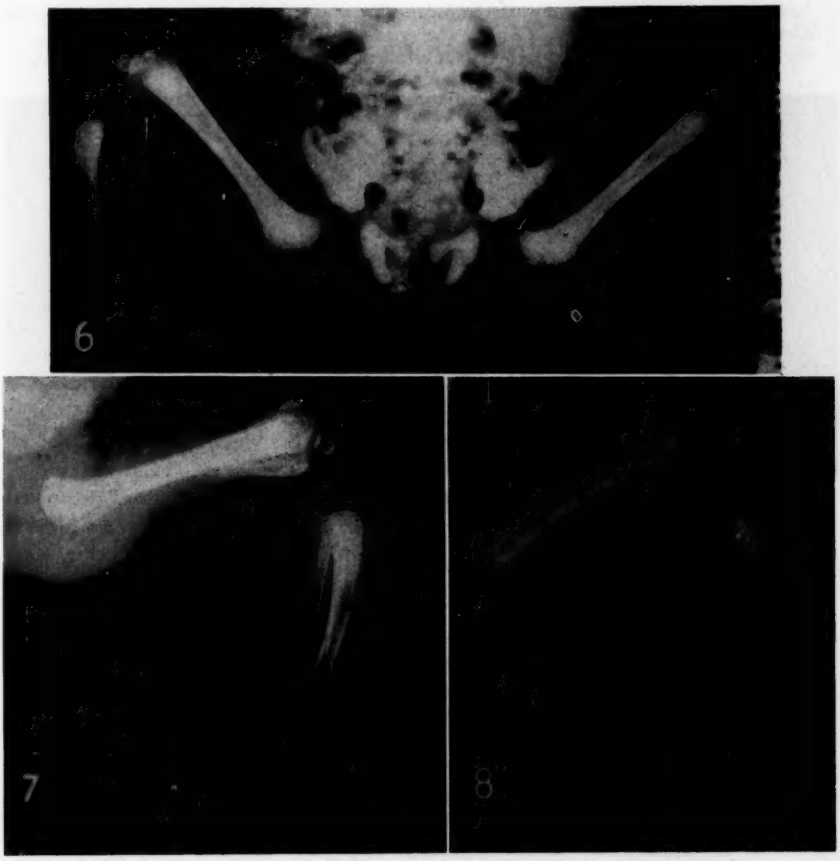

FIG. 6. Case 4, 11 days of age. Osteochondritis and slight subperiosteal changes of lower third of both femora.

FIGS. 7 and 8. Case 4, 16th day of life. Definite subperiosteal calcification of both lower femora. 7. Left. 8. Right.

evidence of healing, with subperiosteal calcification at both lower femora. The possibility of minimal posterior displacement of both lower femoral epiphyses was suggested (Figs. 7 and 8). As part of a general osseous survey, an incidental finding of a healed fracture of the left clavicle was disclosed. Further RGs of the lower extremities showed moderate recalcification of lower femora.

Blood examination showed a blood sugar of 69 mg./100 cc., Ca of 8.7 mg./100 cc., urea nitrogen of 12.3 mg./100 cc. and a vitamin C blood level of 0.22 mg./100 cc. Wassermann, Hinton and Kline tests, as well as blood Wassermann tests on both parents, were negative.

The temperature, which was 37.2°C. on admission, rose to 38.2° on 2nd day, returned to normal on 3rd day and remained normal for the rest of the hospital stay.

Patient was given intramuscular injections of penicillin every 3 hr. for the 1st 15 days. Five days after admission the infant had 3 generalized convulsions. The blood Ca was reported to be 5.6 mg./100 cc. Calcium gluconate, given intravenously, controlled the seizures, and oral Ca was continued until discharge.

Course was one of progressive improvement, with RGs showing calcifying subperiosteal healing of both femora. The patient was discharged 18 days after admission in excellent condition, with full painless motion of both legs.

At 8 wk., RGs showed bilateral subperiosteal calcification extending from distal femoral epiphysis

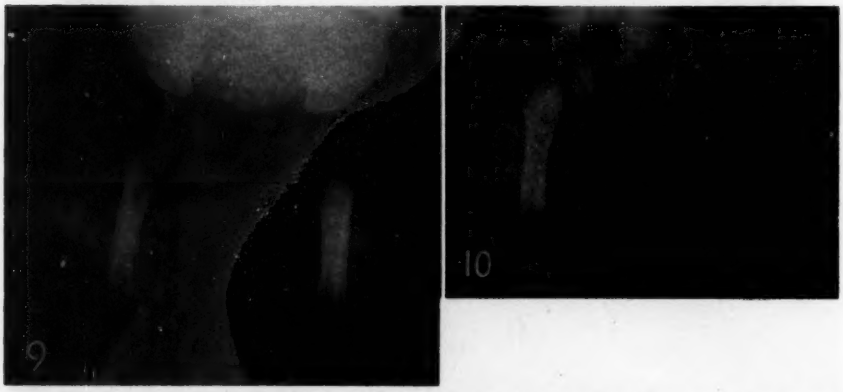

FIG. 9. Case 4, 8 wk. of age. Bilateral subperiosteal calcification extending from distal femoral epiphyses to upper third of shafts. Fusion of cortex and subperiosteal calcification is part of healing process.

FIG. 10. Case 4, 4 mo. of age. Complete resorption of subperiosteal calcification with some thickening of femoral cortices bilaterally.

bilaterally to upper 3rd of shafts of the femora. Fusion of cortex and subperiosteal calcification indicated the healing process (Fig. 9). At 4 mo. RGs show complete resorption of subperiosteal calcification, with some thickening of femoral cortices, bilaterally (Fig. 10).

DISCUSSION

During the delivery or decomposition of the presenting breech, manipulation of the extremities is necessary. Snedecor and Wilson[3] and Kennedy[1] agree that strong torsion and traction can be directly responsible for these injuries. Obletz and Casagrande,[5] in discussing traumatic displacement of the lower femoral epiphyses, feel that a strong backward force on the extended knee produces a rupture of the anterior portion of the periosteal cuff at the lower femoral epiphysis. Significantly, 20 of the 21 cases reported by Kennedy[1] occurred during breech presentation and extraction, or breech alteration and extraction. Likewise, of the 11 cases reported by Snedecor and Wilson[3] all were direct breech or podalic version. Of the four cases reviewed by Burman and Langsam,[6] all were breech presentations, and of the three cases in the newborn infant reported by Obletz and Casagrande[5] two were breech presentations. Of the four cases herein reported, all were direct or altered breech extractions.

The relationship of parity to epiphyseal birth injury in breech extractions seems to be an intimate one. Of the 11 cases reported by Snedecor and Wilson,[3] all the infants

were born of primiparous women. Likewise, the four cases reviewed by Burman and Langsam[6] occurred in primiparous mothers. Of the four cases presented by the authors, three were offsprings of primiparous mothers. On the other hand, breech delivery of itself is not unusually frequent in first pregnancies. One may infer that the unyielding soft parts of a primiparous mother, in the presence of a breech presentation, add to the stress of the delivery necessitating the application of additional force and pull on the part of the attending physician. This may result in epiphyseal or other injuries. In addition, haste to deliver the after-coming head may lead to forceful traction, and its attendant complications.

The underlying nature of the lesions described consists of periosteal elevation, starting at the epiphyseal line and extending as far as the opposite end of the involved bone. The resultant hemorrhage lifts the periosteum and ultimately this subperiosteal extravasation results in the clinical picture described. By the fifth day, callous replaces the hemorrhage and RGs reveal the calcium-containing healing process, often appearing as an ossifying periostotic sleeve. By the time there is roentgenographic evidence of callous formation, the clinical picture improves, and there is beginning painless motion of the affected limb. Serial films show gradual complete resorption of the callous, which may take as long as six months.

In general, no specific therapy is necessary where there is no apparent displacement of the involved epiphysis. The affected extremity is splinted by the patient in the early stages of the injury, and as the hemorrhage is replaced by callous, the swelling subsides, and active motion is begun. Truesdell[7] states that the epiphyses are regularly reunited with their shafts and the affected bones completely restored in form and function, with the exception of the lower femoral epiphysis. With minimal displacement of the epiphysis, no intervention is needed. However, where the displacement is marked, orthopedic care is necessary. The replacement of the dislocated epiphysis should be attempted and an appropriate immobilization of the affected limb should be maintained until adequate healing has taken place.

The possibility of withdrawal of calcium from the circulating blood during the phase of callous formation must be considered. A resultant hypocalcemic tetany may precipitate convulsions as demonstrated in Case 4. Intravenous calcium was used to control this complication.

Summary

Four cases of epiphyseal birth injuries in direct or altered breech extractions are presented. Characteristic roentgenographic studies demonstrate the local findings. The role of parity in the occurrence of these injuries is discussed. The mechanism of the injury, pathology and therapy of epiphyseal birth injuries is reviewed.

Acknowledgment

Acknowledgment is given to Dr. Charles A. Weymuller for permission to include Case 4, and to Dr. John J. Sperandeo for permission to include Case 3.

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SPANISH ABSTRACT

Traumatismo de las Epifisís en los Partos de Nalgas

Durante el curso de una extracción de nalgas o en las presentaciones de nalgas con versión y extracción, la posibilidad de un traumatismo de las extremidades del recién nacido puede ser una complicacion de importancia. El traumatismo puede causar la separación de la epifisís, con ó sin dislocación aparente de la extremidad afectada. Cuando el traumatismo ocurre en la epifisís superior o inferior del femur, ciertos cambios toman lugar, los cuales resultan en un cuadro clinico patológico caracteristico. Usualmente no se sospecha el traumatismo hasta el segundo día de nacido, cuando el niño asume una posición de rana, "frog position," con la extremidad afectada flexionada en la rodilla y la cadera presentando una rotación externa. Los tejidos blandos sobre la region afectada estan tensos y a veces inflamados. Los movimientos pasivos de la extremidad afectada causan un dolar profundo. El paciente está extremadamente molesto y puede presentar una temperatura baja. Las radiografías, negativas durante los primeros cinco días de nacido, comienzan mas tarde a revelar alteraciones subperiosticas con calcificaciones localizadas de sangre extravasada en el sitio del traumatismo.

Un cuadro clinico similar se observa cuando el traumatismo ocurre en las extremidades superiores. En este tipo la extremidad afectada esta flácida, en extensión con rotación externa. Los movimientos pasivos no producen dolor. El traumatismo usualmente afecta la epifisís humeral superior y los tejidos blandos que la cubren estan inflamados produciendo una alteración del contorno normal del hombro. Los cambios radiológicos son similares a los observados en la extremidad inferior.

El mecanismo de estos traumatismos parece ser dependiente del problema de sufrimiento del niño durante la extracción. Durante el parto o en la versión de las presentaciones de nalgas, la manipulación de las extremidades se hace necesaria.

La patología en estos casos consiste en el desgarramiento del periostio, comenzando en la linea epifiseal y extendiendose a veces hasta el extremo oquesto del hueso afectado. La hemorragia resultante produce una elevación del periostio y finalmente esta extravasación subperiostal resulta en el cuadro clinico descrito. Aproximadamente al quinto dia un callo óseo substituye a la hemorragia y es entonces que las radiografias comienzan a revelar el calcio contenido en el proceso de cicatrización. Coincidiendo con la aparición de evidencia radiológica de formación de callo óseo, el cuadro clinico comienza a mejorar y se nota la ausencia de dolar en los movimientos de la extremidad afectada.

La relación entre el numero de embarazos de la madre y la ocurrencia de traumatismo de las epifisís en las presentaciones de nalgas parece ser de naturaleza intima. Se señala como posible que la solidez de los tejidos blandos de una primipara, en presencia de una presentación de nalgas, añade mas dificultad al parto siendo necesario de la aplicación de fuerza adicional por parte del medico.

Los autores describen detalladamente cuatro casos de traumatismo epifisiario ocurridos durante extracciones de presentaciones de nalgas.

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THE TESTIS

V. Use of Testicular Biopsies in the Differential Diagnosis of Precocious Puberty

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PRECOCIOUS masculine development in boys often poses a difficult diagnostic problem since abnormal quantities of androgens, having similar somatic effects, may be produced either by the testis or by the adrenal cortex. Most cases belong to the group of idiopathic precocity, as there is no demonstrable lesion. A smaller number of instances are due to an abnormality in the central nervous system, leading to premature "release" of pituitary gonadotrophins; to an interstitial cell tumor of the testis, or to hyperplasia or neoplasia of the adrenal cortex.

The diagnostic problem usually is that of determining whether the primary cause of the precocity is in the central nervous system (with or without a central nervous system lesion) or in the adrenals. Interstitial cell tumors of the testis may be a cause of precocity, but these tumors are usually palpable or lead to unilateral testicular enlargement. Although there are many case reports of precocious puberty in boys,[1-33] none includes more than a brief reference to testicular morphology. Interstitial cell tumors of the testis in children have been described carefully but the reports have seldom included detailed comments on the remnants of normal testicular tissue which may have been present.[34-42] Because the testis is readily accessible for biopsy, the present study was undertaken to determine whether the histologic appearance of the testis would be helpful in establishing the cause of precocity in the individual patient. Biopsy of the testis has been of use in the adult as an aid to the establishment of a diagnosis in sterility and in endocrine disorders.[43-45]

METHODS

The subjects of this report are eight boys with masculine sex precocity. The age at onset of the masculinization ranged from birth to four years. Information about the testes was obtained by testicular biopsy† in six of the children and from autopsy material on the other two. The tissue was fixed in Zenker's or Helly's fluids, cut in paraffin and stained with phloxinemethylene blue or phosphotungstic acid-hematoxylin. Skeletal maturation was estimated by comparison of roentgenograms of the hand and wrist with Todd's standards.[46] The amount of 17-ketosteroid in the urine was determined chemically.[47] Measurements of gonadotrophic hormone (FSH) in the urine were done by bioassay.[48]

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Supported in part by grants from the Commonwealth Fund of New York and the American Cancer Society.

(Received for publication June 17, 1951.)

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† Testicular biopsies were performed by Dr. F. Simmons.

TABLE 1

FINDINGS IN 8 PATIENTS WITH PRECOCIOUS PUBERTY. SECTION A, BOYS WITH TRUE PRECOCITY; SECTION B, BOYS WITH PSEUDO-PRECOCITY OF ADRENAL ORIGIN. AGE GIVEN REFERS TO TIME OF TESTICULAR BIOPSY

No.	Hosp. No.	Age Yr.	Age at Onset	Ht. age Yr.	Wt. age Yr.	Bone age Yr.	Voice	Acne	Musc. dev.	Penis	Testes	Sex Hair	17-KS mg./24 hr.	FSH mu/24 hr.
						Section A True Precocity								
1	MGH 430 244	1-1/2	6 mo.	2-1/2	3-1/4	2-1/2	deep	0	incr.	enl.	not enl.	+	0.1 to 0.2	neg.
2	MGH 455 675	1-1/2	11 mo.	3-1/2	4-1/2	4-1/4	deep	+	incr.	enl.	not enl.	+	0.3	—
3	MGH 681 079	1-9/12	1-3/12 yr.	2	2-3/12	3	husky	+	incr.	enl.	not enl.	+	.4 to .8	neg.
4	MGH 367 206	7-1/4	1-1/2 yr.	9-1/2	10-1/2	11	deep	0	incr.	enl.	enl.	+	1.2	+4 mu
						Section B Pseudo-Precocity								
5	CH 311 152	1-2/12	birth	1-8/12	obese	—	—	—	well dev.	enl.	not enl.	0	11.0	—
6	MGH 366 552	4-10/12	2 mo.	5-1/2	5-1/2	11-1/2	deep	+	fair	enl.	not enl.	+	12.5	neg.
7	MGH 551 905	5-7/12	4 yr.	8-9/12	6-9/12	10	deep	0	av.	enl.	not enl.	+	20.0	—
8	PBB	11	10 mo.	15-1/2	16+	—	deep	+	well dev.	enl.	—	++	—	—

Observations

A. True Precocious Puberty:

The findings in four boys with true precocious puberty are presented in section A of table 1.

1. Incomplete True Precocity.—The first three patients of this group had incomplete precocity. Masculinization became evident during the first two years of life. The children were tall for their ages, heavy and muscular. The bone age was advanced, attesting the effect of androgens on skeletal maturation.[49] They had deep voices, pubic hair and marked enlargement of the penis; two of them had acne. Although development of the scrotum gave the impression of testicular growth, palpation of the testes did not demonstrate them to be appreciably enlarged.

The 17-ketosteroid values (0.1 to 1.2 mg./24 hr.) were within normal limits or at the most slightly elevated for boys of these ages.[50] The assay for gonadotrophins in the urine was negative in the two patients tested (Nos. 1 and 3).

None of these patients had clinical evidence of neurologic disease. A pneumoencephalogram on one of them (Case 1) revealed no abnormality. Patients 1 and 2 were subjected to laparotomy in search of adrenal tumor or hyperplasia. The adrenals were grossly and microscopically normal in both children.

Testicular biopsies were performed when the patients were 18 to 21 mo. of age. The biopsy material in each child showed partial development of the tubules and an impressive number of large cells in the interstitial tissue.

In the first patient (Fig. 1) the diameter of the tubules was much greater than normal for the age of the child, and lumens had formed. The nuclei of the tubular syncytium were enlarged, with dispersed chromatin granules and many of them contained plasmosomes. The germ cells showed little activity, but a few spermatocytes were present. The tubules were widely separated by large cells arranged in masses and short cords in the interstitial tissue. These cells had a granular, eosinophilic cytoplasm that occasionally contained fine vacuoles. The cells most closely simulated the cells that arise in the interstitial tissue of a eunuchoid patient as a response to treatment with chorionic gonadotrophin (APL), which resembles luteinizing hormone.[51]

The testicular biopsy in Case 2 resembled that of the first patient but was even more advanced in its development (Fig. 2). The syncytium and nuclei of the enlarged tubules approached the appearance of adult Sertoli cells, although no crystalloids or fat droplets had formed in the cytoplasm. Germ cells and spermatocytes were more numerous than in the testis of the first patient. The interstitial tissue was loosely arranged, as in the adult, and small groups of large interstitial cells were sparsely scattered through the intertubular spaces. A few of these cells contained fine droplets but none contained pigment or crystalloids.

In Case 3 there was a marked increase in the diameter of the tubules and lumens had developed (Fig. 3). The Sertoli cells were partially differentiated and their cytoplasm contained many "fibrils." The spermatogonia had increased in number beyond the normal for the age of the patient; a few primary spermatocytes had developed. The interstitial tissue contained many groups of large polygonal cells with a granular, eosinophilic cytoplasm. Frequently fine vacuoles or coarse golden-brown pigment granules were present in the cytoplasm.

2. Complete True Precocity.—Patient 4 had complete precocity. On physical examination he differed from the first three patients only in that his testes were enlarged. His

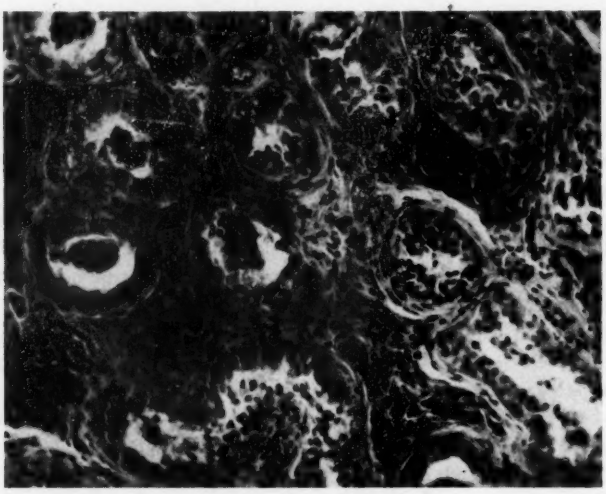

FIG. 1. Case 1, aged 1½ yr. Incomplete true precocity. Tubules are abnormally large and have developed lumens. Masses of large interstitial cells separate tubules. (Compare with normal, Figs. 5 and 6.) ×200.

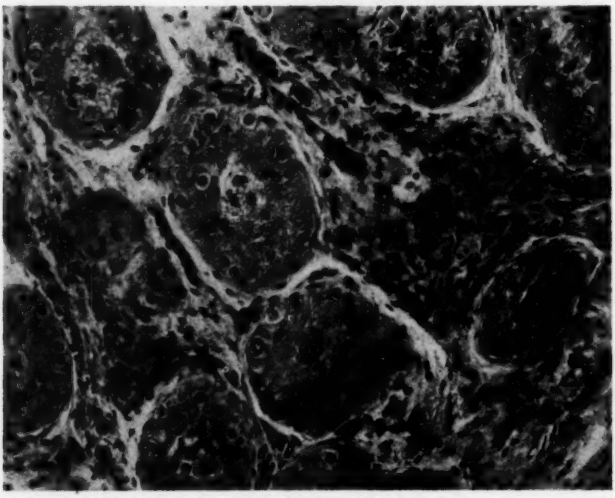

FIG. 2. Case 2. Incomplete true precocity. Testicular biopsy at age 1½ yr. Tubules are abnormally large and are lined by partially developed Sertoli cells. Germ cells are unusually numerous. Several groups of interstitial cells are illustrated. ×200.

17-ketosteroid excretion was nevertheless relatively low. When the child was 9 years of age the urinary FSH assay was positive (4 mouse units/24 hr.). His pneumoencephalogram was normal. His adrenal glands were not explored.

The testicular biopsy was performed when the child was 7 years of age. The tubules

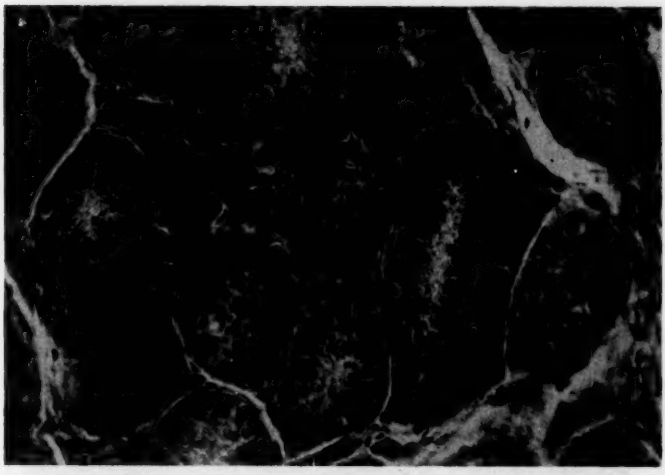

FIG. 3. Case 3. Incomplete true precocity. Testicular biopsy at age 1 9/12 yr. Tubules are enlarged and there is precocious development of Sertoli cells. Masses of interstitial cells are present. ×200.

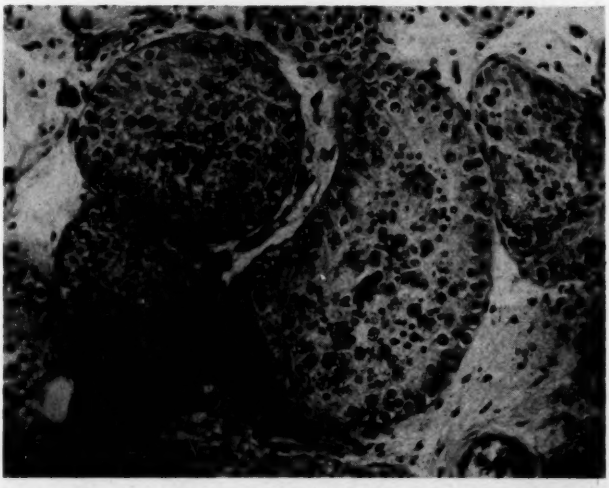

FIG. 4. Case 4. Complete true precocity. Testicular biopsy at age 7 yr. Tubules are fully developed and contain sperm. Leydig cells are not present in this area. ×200.

were mature, with all members of the spermatogenic line represented in large numbers, including a moderate number of well-formed sperm (Fig. 4). The Sertoli cells were fully developed. The interstitial tissue resembled that of a mature testis. Small groups of large cells were scattered throughout. They showed both fine and coarse cytoplasmic granules and some of them contained vacuoles. A second biopsy taken two years later presented the same picture.

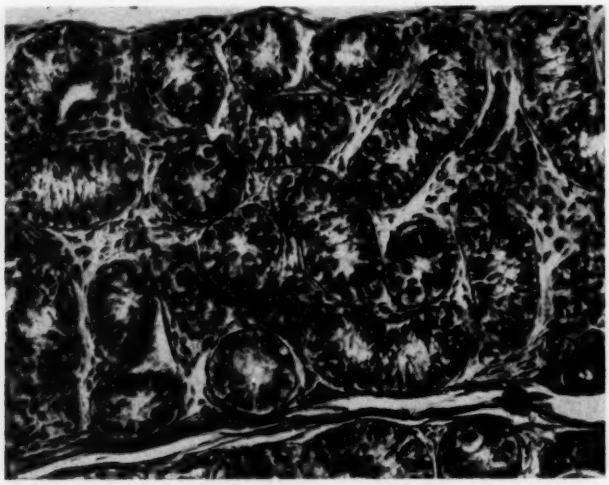

FIG. 5. Normal testis at 2 yr. of age. Testicular cords have not developed lumens and are composed of syncytium containing small, deeply staining nuclei without visible nucleoli. Few large, inactive germ cells are present. No large interstitial cells. ×200.

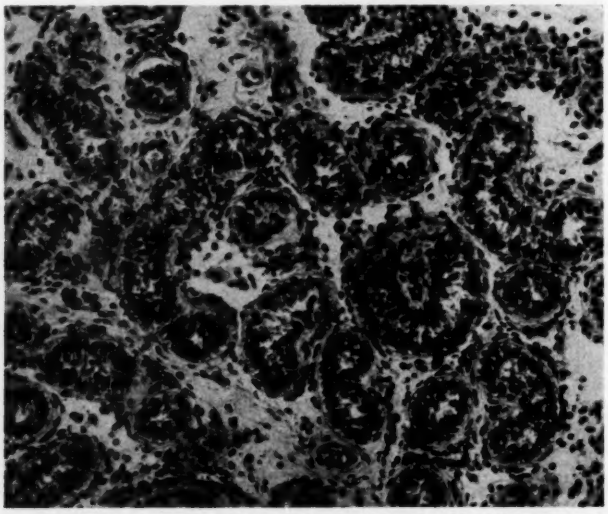

FIG. 6. Normal testis at 6 yr. of age. No visible sign of maturation. (Compare with Figs. 5 and 7.) ×200.

COMMENT

Excepting the first few weeks of life, the morphology of the normal testis during childhood shows little qualitative change until puberty. During the neonatal period the large interstitial cells, which form a prominent feature of the fetal testis, undergo relatively rapid involution and degenerative change. In timing and character this phenomenon is

similar to the involution of the fetal adrenal cortex.[52] The picture then remains static, the volumetric increase in the testis being accounted for by lengthening of the sex cords.

During this period of quiescence the testis is composed of tortuous cords segregated into lobules and imbedded in a fibrous interstitial tissue (Fig. 5). The cords consist for the most part of a syncytium with finely granular cytoplasm in which several layers of small oval nuclei are oriented perpendicularly. The germ cells of the cord are conspicuous because of their size and the clarity of the cell boundary. During infancy they are almost inactive, although a few mitoses can usually be found. The cord is enveloped by a delicate basement membrane and by the tunica propria. No large interstitial cells are present. Very little morphologic change takes place in the gland until adolescence (Fig. 6). At the

FIG. 7. Normal testis at 13 yr. of age. Tubules are enlarging and Sertoli cells are almost fully developed. Mitotic activity in germ cells and few primary spermatocytes are present. No Leydig cells are visible. ×200.

beginning of adolescence the testis begins to metamorphose towards its adult form (Fig. 7). The sex cords enlarge from an initial diameter of approximately 55 μ and with ever-increasing number develop lumens, thus becoming true tubules which measure approximately 200 μ in diameter when mature. At the same time the undifferentiated nuclei in the syncytium of the tubule hypertrophy and become round, the nucleoprotein granules become less densely packed, and prominent plasmosomes appear. Concomitantly the cytoplasm of the syncytium increases in volume. Crystalloids and fat droplets appear when spermiogenesis is established. The syncytium now resembles the mature Sertoli cytoplasm. The spermatogonia show a marked increase in mitotic activity at approximately 11 years of age and during the next 4 to 5 years spermatogenesis gradually reaches adult proportions. Recognizable Leydig cells do not appear in the interstitial tissue until about the 14th year, which is well beyond the age at which adolescence is initiated.

The histologic appearance of the testes of the first three patients had a common theme but varied in detail. They all showed partial development of the tubules and a significant number of large interstitial cells. In the fourth patient the tubules were mature, there was

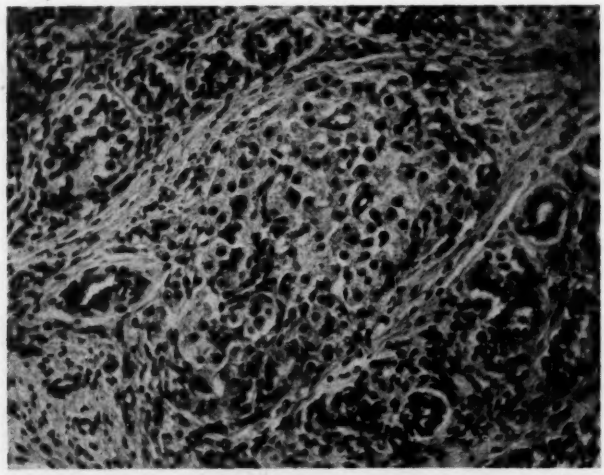

FIG. 8. Case 5. Pseudoprecocious puberty with hyperplasia of adrenal cortex. Testis as 1 2/12 yr. One-of groups of large interstitial cells is illustrated. Tubules are quiescent and immature. ×200.

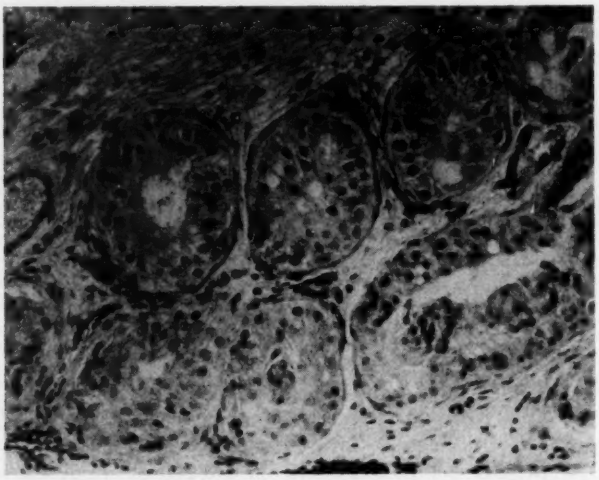

FIG. 9. Case 6. Pseudoprecocious puberty with hyperplasia of adrenal cortex. Testicular biopsy at age 7 yr. There is marked enlargement of tubules and they are lined by mature Sertoli cells. Germ cells show minimal activity. No large interstitial cells are present between tubules. ×200.

active spermatogenesis and the interstitial tissue contained fully developed Leydig cells.

The interstitial cells of the testis normally begin to produce androgens between 11 and 14 years, when these cells presumably become subject to the influence of pituitary interstitial cell-stimulating hormone. Tubular maturation is completed under the influence of pituitary follicle-stimulating hormone. The excretion of gonadotrophic hormones in the urine generally reaches levels which can be detected by bioassay at about 12 years of age.

In these patients the precocity apparently was due to premature stimulation of the

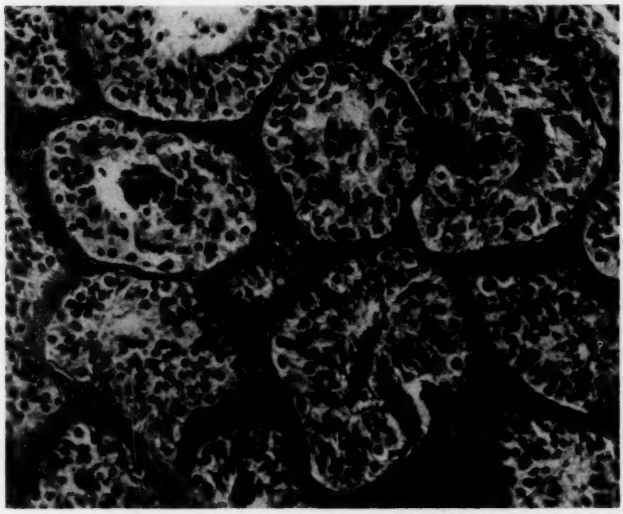

FIG. 10. Case 7. Pseudoprecocious puberty with hypertrophy of adrenal glands. Testicular biopsy at age 5½ yr. Tubular enlargement with development of lumens. Sertoli cells have partially differentiated but germ cells are inactive. No large interstitial cells are present. ×200.

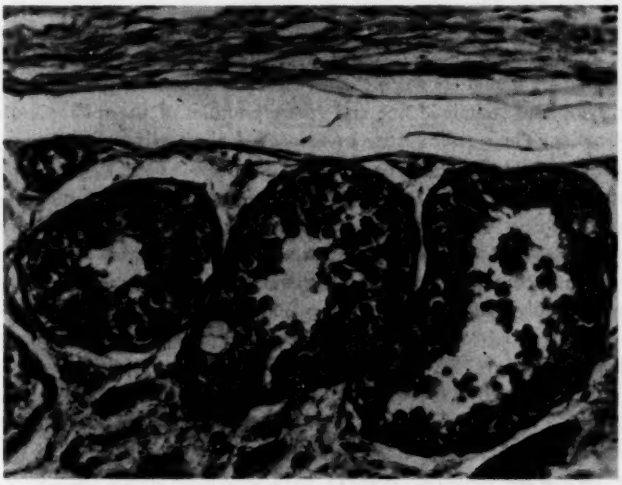

FIG. 11. Case 8. Pseudoprecocious puberty with carcinoma of adrenal cortex. Testis at 11 yr. of age. Spermatocytogenesis is unusually active. No Leydig cells. ×200.

testes by pituitary gonadotrophic hormones. In the first three patients, whose precocity was partial in that there was no spermatogenesis, it is possible that the stimulation came from interstitial cell-stimulating hormore alone and that there was no secretion of follicle-stimulating hormone. In two of these children no gonadotrophins could be demonstrated in the urine. In the fourth child, whose precocity was complete, the urine contained measurable amounts of gonadotrophin.

Premature production of pituitary gonadotrophic hormones is known to be initiated in some instances by a lesion in the central nervous system, in the region of the supraoptic and paraventricular hypothalamic nuclei.[1-4] If such a lesion was present in any of these children it was so small as to produce no other disturbances during the years through which the patients have been followed. It is of interest that in the family of Patient 3 there were several instances of very early masculinization in individuals who have grown to normal adulthood.

B. Pseudoprecocious Puberty:

Section B of table 1 summarizes the findings in four boys whose masculinization was due to disease of the adrenal cortex.

1. Hyperplasia of the adrenal cortex.

a. Hyperplasia with metabolic disturbances. Patients 5 and 6 had an early onset of masculinization associated with symptoms suggestive of insufficiency of the adrenal salt-regulating hormone. In both patients the evidences of need for desoxycorticosterone and sodium chloride became manifest shortly after birth.

Patient 5* died at the age of 14 months in Addisonian-like crisis. The 17-ketosteroid excretion at this time was 11.0 mg./24 hr. At the time of death he was tall for his age and had well-developed muscles. The penis was enlarged, the testes were small and there was no pubic or axillary hair. Both adrenal glands were enlarged and showed hyperplasia of the inner cortex. The testes were not grossly enlarged. Microscopic examination of the testes showed that both the tubules and the interstitial tissue were normal for the age of the patient: there was no evidence of premature development (Fig. 8). At the rete and lying in the interlobular connective tissue were several groups of cells, each filling the area encompassed by a high power field. These cells were arranged in short branching cords. Their cytoplasm contained fine and coarse granules of precipitate and many small and large vacuoles. Their resemblance to adrenal cortical cells was striking.

The clinical details for Patient 6 have been reported.[53, 54] Signs of adrenal insufficiency appeared shortly after birth and masculinization became evident at 2 months of age. He was tall for his age in early childhood and had extremely good musculature. Skeletal maturation progressed so rapidly that growth ceased when he was about eight years old. The growth of the penis was rapid and excessive. The testes were not enlarged for some years but subsequently grew rapidly and became unusually firm. The excretion of 17-ketosteroids became progressively greater. It was 12.5 mg./24 hr. when he was 4 10/12 years of age and 200 mg./24 hr. when he was 8 years of age. At this time there was no measurable gonadotrophin in the urine. Adrenal biopsy showed hyperplasia of the zona reticularis.

This patient has been followed since early infancy and is now about 12 years old. During this period six testicular biopsies have been performed. Microscopic sections demonstrated a gradual compression and obliteration of the pre-existing glandular tissue by a steadily increasing mass composed of elements resembling adrenal cortical cells. From the beginning it was evident that these cells were independent of the remaining testicular tissue. However, the few remaining tubules showed definite changes. In the first biopsy, at the age of 4 10/12 years, the tubules were unusually large and had lumens,

* The authors wish to thank Dr. Sidney Farber of The Children's Medical Center in Boston for permission to publish the findings on this patient.

but the cells lining them were infantile. Within a year the tubules were approximately twice the normal diameter (Fig. 9). The Sertoli cells were fully developed and contained cytoplasmic crystalloids and fat droplets. This development was not reflected in the germ cells, which remained quiescent. No large cells were found in the interstitial tissue associated with the tubules in any of the biopsies.

b. Hyperplasia without metabolic disturbances. Patient 7 developed secondary sex characteristics when he was 4 years of age. At 5½ years he was relatively tall for his age but his muscular development was not unusual. His voice was deep; he had pubic hair and a large penis. The testes were only slightly enlarged. His skeletal maturation was advanced. The urine contained 20 mg. of 17-ketosteroids in 24 hours. Exploration of the adrenal glands showed gross hypertrophy bilaterally. A subsequent testicular biopsy showed an increase in tubular diameter far beyond the normal. The tubules had developed lumens and there was partial differentiation of the lining cells towards Sertoli cells. There was, however, no activity in the germ cells and the interstitial tissue was totally fibrous (Fig. 10).

2. Malignancy of the adrenal cortex. The clinical details and a discussion of the last case (No. 8) have been reported by Quinby.*[22] The patient manifested virilism at the age of 10 months. He grew rapidly and was very muscular. He died at the age of 11 years from carcinoma of the left adrenal gland with widespread metastases. The opposite adrenal had become atrophic. There were no studies of urinary hormone levels. At post mortem the tubules of the testes showed more spermatogenic activity than is usual for normal children of the same age and some of the tubules contained sperm. In contrast to the maturation of the tubules, there was no enlargement of the interstitial cells (Fig. 11).

Comment

The adrenals usually begin to secrete the precursors of 17-ketosteroids at about 8 to 10 years of age (the "adrenarche"[55]) at which time approximately 1 mg. of 17-ketosteroids a day appear in the urine. These secretions cause the development of pubic and axillary hair and of acne in girls and contribute to their development in boys. They do not appear to be truly androgenic in normal persons, as they fail to induce development of the secondary sex characteristics of eunuchoid men, or to cause clitoral hypertrophy or other signs of masculinization in normal women or in women with ovarian agenesis.[56] The 17-ketosteroid excretion of the present patients was high, but not in excess of the amount excreted by many normal women. The urinary 17-ketosteroids of several patients with adrenal virilism have been subjected to chromatographic analysis and have been found to produce a pattern different from that of normal individuals.[57] This finding suggests the possibility of an abnormal type of 17-ketosteroid precursor being responsible for precocious masculinization in adrenal virilism, rather than an unusually early production of normal cortical "androgens."

Discussion

The eight cases described above represent two types of premature masculinization. Of the four patients with true precocity, three had the incomplete form of the disorder, with

* The authors wish to thank Dr. Samuel P. Hicks of the Peter Bent Brigham Hospital in Boston for permission to publish the findings on this patient.

stimulation primarily of the interstitial tissue of the testis while in the fourth child testicular development was complete. The other four patients had pseudoprecocity which resulted from disease of the adrenal cortex. Reference to the table will show that the eight patients resembled each other closely physically. The testes were small in comparison to the development of the penis and scrotum in all the children except Patient 4 in whom precocity was complete, and Patient 6 in whom growth of aberrant "adrenal cells" in the testes led to testicular enlargement. The discrepancy between testicular size and degree of masculinization can be accounted for by the fact that the greatest bulk of the mature testis is due to growth of the tubules, while the Leydig cells, which produce the masculinizing hormone, contribute little to the size of the testis. The presence of associated metabolic disturbances in Patients 5 and 6 served to implicate the adrenal gland. In the other six children the source of masculinizing hormone was not readily apparent from the preliminary examinations.

Gonadotrophic hormone was detectable in the urine only in the patient with complete precocity, and so does not serve to differentiate true precocity from pseudoprecocity. The 17-ketosteroid excretion was strikingly different in the two groups of patients. The amount excreted was greatly increased in the children with precocity of adrenal cortical origin but was only slightly increased in the children with true precocity. The small output of 17-ketosteroids in true precocity apparently reflects the secretion of very potent androgens.

The information obtained from the testicular biopsies suggests that androgens, whether of Leydig cell or adrenal cortical origin, promote the growth of the tubules and the development of their lumens. In true precocity all elements of the testis are stimulated, Leydig cells are seen in the interstitial tissue and various degrees of spermatogenesis occur. This observation is in keeping with reports that sperm have been found in the ejaculate of young boys.[1-5] In pseudoprecocity, in which masculinization is independent of gonadotrophic hormones, the Leydig cells are not activated nor does spermatogenesis occur. The tubules, however, undergo partial development in response to the adrenal cortical hormones which have caused the somatic development.

In the literature there are two reports of presumed spermatogenesis in adrenal precocity. In 1933 Player and Lisser[24] reported the case of a child almost 5 years of age who had shown precocious development from the age of 1½ years. On prostatic massage the "secretion contained numerous spermatozoids and much lecithin." A 278 gm. tumor was removed successfully from above the left kidney. There was comparatively little change in the child's physical status after removal of the tumor, but the sperm disappeared from the fluid obtained by prostatic massage. Seckel,[4] in an article on precocious sexual development in children, notes that spermatogenesis has been reported twice in association with adrenal tumors: this number probably includes the case of Player and Lisser. As far as we are aware adrenal androgens do not stimulate the interstitial tissue of the testis, although they may stimulate the testicular tubules. Bulloch and Sequeira[58] in 1905 reported the case of an 11 year old girl who had started "menstruating" some 15 months before her death. The child showed changes that were somewhat similar to those found in Cushing's syndrome and died of an adrenal carcinoma with metastases. The uterus was enlarged and the ovaries were "perhaps a little larger than normal. On section several corpora lutea were found, one being of recent date." This description seems to indicate both a follicle-stimulating and a luteinizing effect on the ovaries, but there is nothing to indicate that this stimulus may not have originated in the anterior pituitary,

as is often the case in normal girls of this age. Unfortunately no description of the microscopic findings was included.

In the present authors' material there is no case of an active interstitial-cell tumor of the testis in childhood. The descriptions of such cases in the literature indicate that the tubules were either infantile and inactive or that they had undergone pressure atrophy. However, Stewart, Bell and Roehlke[36] reported a boy 4 years of age with precocious somatic development apparently due to a small interstitial cell tumor in one testis. The tubules of this testis showed premature development and pronounced spermatogenic activity without actual sperm formation. No change had taken place in the interstitial tissue apart from the tumor. The activity in the tubules suggests the capacity of androgens, of whatever origin, to stimulate the development of the testicular tubules. Kinsell[59] reported a 24 year old man, with probable panhypopituitarism, in whom spermatogenesis occurred while he was receiving testosterone therapy. In the present investigators' group of patients there was no evidence of germ cell stimulation in precocity of adrenal origin, with the possible exception of the 11 year old boy with carcinoma of the adrenal in whom spermatogenic activity seemed to be unusually well developed.

Summary

The history, physical appearance and laboratory studies performed on eight boys with premature masculinization are presented. The histologic appearance of their testicular tissue is described. Four of the patients had true precocious puberty, which was complete in one and incomplete in three of them. Four had pseudoprecocious puberty, due to adrenal hyperplasia in three of the patients; two of these had associated metabolic disturbances; in the fourth child pseudoprecocity resulted from an adrenal cortical carcinoma.

Comparison of the two groups of patients shows that physically they are similar, although bilateral enlargement of the testes or metabolic disturbances in some instances may indicate the source of the precocity. The children with adrenal virilism excreted large amounts of 17-ketosteroids, possibly arising from abnormal precursors, while the patients with true precocity excreted only small amounts of 17-ketosteroids. The observations further suggest that testicular biopsy may be a simple additional means of distinguishing between true precocity and adrenal precocity. In the former the stimulation seems to be all inclusive with respect to the gonads, leading to the development of large interstitial cells and to tubular maturation and spermatogenic activity of varying degree. In precocity of adrenal origin the interstitial cells do not develop. The appearance of the interstitial cells is apparently the essential feature which differentiates the histology of the testis in these two conditions.

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SPANISH ABSTRACT

El Uso de la Biopsia Testicular en el Diagnóstico Diferencial de la Pubertad Precoz

Se presenta la historia clinica, examen fisico y los estudios de laboratorio realizados en ocho niños con masculinización prematura. Se describe la apariencia histologica del tejido testicular. Cuatro de los pacientes presentaban una pubertad precoz verdadera, la cual fué completa en un caso é incompleta en tres casos. Cuatro pacientes presentaban una pubertad pseudoprecoz debida a una hiperplasia

suprarenal en tres casos, dos de los cuales tenian alteraciones metabolicas asociadas. El cuarto paciente presentaba una pseudoprecocidad producida por un carcinoma de la corteza suprarenal.

La comparación de los dos grupos de pacientes demostró que ambos fueron fisicamente similares, aunque a veces, la hipertrofia testicular o las alteraciones metabolicas pueden indicar el origen de la precocidad. Los niños con virilismo adrenal excretaron cantidades grandes de 17-ketoesteroides, posiblemente originados de precursores anormales, mientras que los pacientes con precocidad verdadera solo excretaron pequeñas cantidades de 17-ketoesteroides. Se estima que la biopsia testicular puede ser un metodo simple adicional para la distinción entre la precocidad verdadera y la precocidad de tipo suprarenal. En la primera la estimulación de los testiculos es general con respecto a las gonadas, causando el desarrollo de celulas intersticiales de gran tamaño, maduración tubular y aumento de la actividad espermatogenetica de grados variables. En la precocidad de origen suprarenal las celulas intersticiales no se desarrollan. La presencia de celulas intersticiales constituye el factor esencial en el cual se basa la distinción histologica entre estas dos condiciones.

300 Longwood Avenue

Pediatrics

VOLUME 8 NOVEMBER 1951 NUMBER 5

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

AMERICAN ACADEMY OF PEDIATRICS

STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS FOR THE FISCAL YEAR ENDED JUNE 30, 1951

Cash Receipts:		
Dues		$72,745.62
Initiation Fees		10,550.25
Annual Meetings:		
Chicago—October 1950:		
Registration	$17,270.00	
Round Tables	4,161.00	
Seminars	2,225.00	
Exhibits	7,555.00	31,211.00
Toronto—October 1951:		
Exhibits		6,946.00
Areal Meetings:		
Cincinnati—March 1951:		
Registration	4,595.00	
Clinics	701.00	
Exhibits	9,690.00	14,986.00
PEDIATRICS—Subscriptions	26,350.00	
—Special Account—Publisher's Refund	10,070.85	36,420.85
Pamphlets—Child Health Records	556.65	
Immunization Procedures	24.59	
Newborn Manual	742.77	1,324.01
Interest Earned		1,302.34
Sale of Equipment of ICH Committee		412.50
International Congress Assessment		10.00

Contributions:			
National Foundation for Infantile Paralysis, Inc.:			
For Improvement of Child Health	3,333.33		
For Committee on Medical Education	6,150.00		
For Committee on Medical Education to Publish Reports	516.67		
American Legion Auxiliary, Inc. of the Dept. of N.Y.—For Tumor Registry	2,500.00		
Pet Milk Co.—For Committee on Hospitals and Dispensaries	2,500.00		
Albert H. and Jessie D. Wiggin Foundation	1,500.00		
Eli Lilly & Co. (For Committee on Drug Dosage)	1,000.00		
E. R. Squibb & Sons (For Committee on Drug Dosage)	1,000.00		
G. D. Searle & Co. (For Committee on Drug Dosage)	500.00		
Charles H. Hood Foundation (For Committee on Improvement of Child Health)	1,000.00		
Burroughs Wellcome & Co., Inc.	250.00		
Missouri Study of Child Health Services (For Advisory Committee on Child Health)	305.05	20,555.05	
TOTAL CASH RECEIPTS			$196,463.62
Cash Disbursements:			
Annual Meeting Expenses:			
Chicago—October 1950	$29,828.39		
Toronto—October 1951	1,238.26	$31,066.65	
Areal Meetings:			
Cincinnati—March 1951	9,121.22		
Philadelphia—March and April 1950	5.00		
Washington, D.C.—May 1952	2.44	9,128.66	
Bank Service Charges and Expense		129.27	
Certificates		169.77	
Contingency Fund Expenses		328.84	
Emergency Fund Expenses		436.13	
Committee Expenses:			
Accident Prevention	204.87		
Budget	236.09		
For Cooperation with AMA (Liaison)	129.98		
Geographical Distribution of Pediatricians	116.00		
Hospitals and Dispensaries	1,421.84		
Immunization Procedures	22.01		
Improvement of Child Health	3,751.95		
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Mentally and Physically Handicapped Children	17.72		
Non-Medical Groups	10.34		
Latin American Affairs	10.66		
Program	622.56		
Public Relations	57.08		
School Health	76.23		
Tumor Registry Committee Expense	14.00		
American Cancer Society—For Tumor Registry (Babe Ruth Cancer Fund)	5,978.81		
American Legion Auxiliary, Inc. of Dept. of N.Y.—For Tumor Registry	2,500.00		
Study of Radiation Effects of Childhood	4,000.00	20,876.93	

District Chairmen Expenses		259.98	
Executive Board		9,732.37	
Meetings—General		47.07	
Miscellaneous Expenses		1,062.18	
Office Supplies		518.39	
Office Equipment		4,961.12	
Pamphlets—Child Health Records	414.26		
Immunization Procedures	5.54		
Newborn Manual	497.25	917.05	
PEDIATRICS—Advances for Publishing and Editorial Board Expenses	26,350.00		
—Publishing Committee Expenses Chicago Meeting	535.13	26,885.13	
Publicity—New Members		314.00	
Postage		1,888.66	
Rent and Light		6,774.60	
Employees' Retirement Plan Insurance		4,896.29	
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Executive Secretary	18,000.00		
Executive Secretary-Elect	9,119.99		
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State Chairmen Expenses		177.72	
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Surety Bond Premiums		302.50	
Telephone and Telegraph		696.77	
Travel—Secretary		493.94	
TOTAL CASH DISBURSEMENTS			$175,210.04

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PROVIDING COMPLETE MEDICAL CARE IN EPIDEMIC POLIOMYELITIS

A Symposium

ALEX J. STEIGMAN, M.D., *Chairman*
University of Louisville School of Medicine, Louisville, Ky.

THE TREATMENT OF ACUTE POLIOMYELITIS

PHILIP M. STIMSON, M.D.
New York Hospital, Cornell Medical Center

THE PATIENT IN RELATION TO COMPLETE MEDICAL CARE IN POLIOMYELITIS

WILLIAM T. GREEN, M.D.
Harvard Medical School, Boston

PROVIDING COMPLETE MEDICAL CARE IN POLIOMYELITIS

MOIR P. TANNER
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HOME CARE FOR POLIOMYELITIS PATIENTS

EMIL D. W. HAUSER, M.D.
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INDIANA'S POLIOMYELITIS PLANNING COMMITTEE

LEROY E. BURNEY, M.D.
Indiana State Board of Health, Indianapolis

THE NATIONAL ASPECTS IN PROVIDING COMPLETE MEDICAL CARE IN POLIOMYELITIS

KENNETH S. LANDAUER, M.D.
National Foundation for Infantile Paralysis, New York City

Presented at the Annual Meeting of the American Academy of Pediatrics,
Chicago, Oct. 16-19, 1950

INTRODUCTORY REMARKS

ALEX J. STEIGMAN, M.D.

Fellow Members of the Academy and Guests:

It is particularly appropriate that a Symposium of this kind be held at this time and under the sponsorship of the American Academy of Pediatrics. For the fourth successive year, we are experiencing an unusual incidence of acute anterior poliomyelitis in our country so that by the end of this year it is anticipated that the numbers of cases reported in the 4 year period will exceed 100,000.*

Although the distinguished members of this Panel represent 4 different specialties, it is readily understandable that the Academy of Pediatrics would be the group to sponsor such a program. The disease, while no longer striking infants as markedly as was once the case, still has its highest age specific attack rate in the group aged 5 to 9 years in this country. Pediatricians are expected to keep themselves thoroughly familiar with all the aspects of this disease and, indeed, it is one of the few conditions in which pediatricians are still frequently called to deal with when it strikes adults.

Pediatricians perhaps more than any other specialists in medicine have been acutely aware of the impact of social, economic, legislative and administrative forces upon the things we see and do daily in clinical practice. In few diseases is this more strikingly so than in acute anterior poliomyelitis. Consequently, the contributions of the members of this Panel, representing as they do the fields of pediatrics, orthopedics, organized voluntary health activities, hospital administration and public health, should prove most helpful in answering some of your questions and perhaps in inciting others.

THE TREATMENT OF ACUTE POLIOMYELITIS

PHILIP M. STIMSON, M.D.

In the early stages, the importance of rest and the avoidance of fatigue should be emphasized. Comfort is to be sought and pain relieved, but artificial sleep is dangerous.

The proper regulation of the administration of fluids requires judgment and study. In selected cases, dehydration may be helpful; in others harmful, and on the other hand, flooding a patient intravenously may cause several harmful results.

The causes of breathing difficulty are many and varied and should be clearly understood and differentiated. The respiration may be sufficient to permit adequate oxygenation, but there may be inadequate CO_2 elimination, resulting in respiratory acidosis. Hence, the evaluation of possible carbon dioxide retention is at times vital.

There are 4 general methods of accomplishing artificial respiration: viz., extrathoracic positive pressure; extrathoracic negative pressure; upper respiratory positive pressure; and action on the diaphragm. These methods have different physiologic results. Upper respiratory positive pressure breathing has advantages including helping to establish normal CO_2 elimination.

The rocking bed is useful for artificial respiration when the need for such help is not marked, but for severe breathing difficulty, the tank respirator is indicated. Skill is necessary for the proper use of any respirator, and there are many little "tricks" worth knowing.

There are clear indications for tracheotomy such as bilateral abductor paralysis of the vocal cords, but the more adequate the team caring for their patients, the fewer are other indications. Teams should include a laryngologist, an anesthetist and a biochemist.

Expensive antibiotics are valueless in combatting the polio virus, but may be indicated for polio cases when there is breathing difficulty; when catheterization is necessary; or when the leukocyte count is appreciably elevated.

Good results in polio treatment depend more on wise and skillful medical and nursing care than on minor variations in equipment.

THE PATIENT IN RELATION TO COMPLETE MEDICAL CARE IN POLIOMYELITIS

WILLIAM T. GREEN, M.D.

The plans of care in poliomyelitis must consider primarily patients who have moderate to severe paralysis; the care of those with lesser degrees of involvement will naturally fall into pattern.

* When this Symposium went to press, the total incidence including 1950 was available. For the 4 year period 1947 to 1950 inclusive, the total numbers of cases reported was 113,932.

The two essential features of the disease, in relation to medical care, are that it may kill and it may cripple. Effective treatment does much to change the outcome in both of these particulars. The time of greatest danger to life is in the acute stage in instances where either the bulbar or the spinal respiratory form, or a combination of these two, occurs. The first consideration in any plan of medical care, therefore, is to provide for effective treatment of these forms of the disease, since the character of the treatment often makes the difference between life and death. Hospitals with the needed equipment must be at hand and, beyond all else, doctors and nurses skilled in the treatment of these forms of the disease must be available.

Reduction of the crippling effects of the disease also depends to a great extent upon the efficiency of treatment. Most all patients can be made socially and economically independent, provided they receive their maximal possibility of rehabilitation. In those with little or no paralysis, the problem is ordinarily simple, but in those severely affected the regimen of rehabilitation may be long and arduous.

Attention must be given to the deforming factors from the onset of paralysis. In practice, an orthopedic surgeon, or someone skilled in the diseases of the musculo-skeletal system, should participate in the care of the patient at this early period, and should assume a dominant role once the acute stage is passed. Early, effective, physical therapeutic measures may do much to simplify the rehabilitation. The regime for a given patient must be highly individualized. It is guided by such factors as the location and degree of the paralysis and the amount of sensitivity and tendency to contracture. It considers the stages of the disease, and is guided by the progress of the patient. Activities are carefully supervised and graduated to the capabilities of the patients. The measures of rehabilitation follow a progressive schedule.

The details and elaborateness of the set-up for the care of the disease in any area will vary, depending upon local factors. Plans of care must consider not only the therapy during periods of hospitalization, but home care as well. In most patients, in fact, the major part of the convalescent therapy can be carried out in the home, after the patients' treatment is stabilized. A mother who is well instructed and supervised makes an excellent physical therapist. Outpatient facilities for regular supervision and treatment should be available. These should be integrated with the provision for hospital care and with the organized supervision of care in the home.

The necessity of treatment and the possibilities of rehabilitation are not terminated by the end of the convalescent stage or period of so-called spontaneous recovery of musculature. In children, in particular, deformities may develop during this period. Periodic supervision is necessary during the growing period and relatively simple maneuvers may obviate deformity. Furthermore, much can be done in the "chronic stage" by functional training and by surgery. The objective is to make the patient as good as he can be with the residual involvement which exists.

The human factors must be emphasized in all phases of therapy. Emotional adjustment must be guided by all individuals concerned with the care of the patient. Fortunately, the degree of recovery which will ensue is determined gradually, so that the patient has time for adaptation to his residual state. Adults and those in late adolescence present the maximal problems in this field.

The patient with residual involvement must be guided into a vocation which considers his physical handicaps in relation to his attributes. Guidance should be developed as the patient's limitations are defined.

PROVIDING COMPLETE MEDICAL CARE IN POLIOMYELITIS

MOIR P. TANNER

The administrator's responsibilities in providing care for polio cases cut across all phases of the hospital experience.

Sufficient respirators, in perfect mechanical condition, adequate equipment for tracheotomies, oxygen and suction, hot pack machines, bed boards, foot boards and other equipment must be immediately available. It is even more important that there be sufficiently qualified people behind this equipment.

It is his responsibility to determine the availability of either House or Attending Staff for emergency procedures; specially trained nurses for polio, tracheotomies, lung cases, etc., are essential, and he should be alert to the possibilities of "group nursing."

If outpatient screening centers are required, administration must provide them. The administrator

must be close to the local chapter of the National Foundation for Infantile Paralysis and other groups in the field, and must know exactly the financial help available and be responsible for the dispensing of this information through Admissions, Social Service and other sources.

The administrator must have more than a smattering of knowledge regarding technics for the general hospital, must provide adequate space, equipment and personnel on short notice. Part of our administrative job is to convince more community hospitals that they have a responsibility regarding the admission of polio patients.

A polio committee of the staff can be of tremendous value, making recommendations to the Medical and Governing Boards regarding curtailment of elective surgery, the responsibility of pediatrics and orthopedics, the question of neurologic consultations, the providing of convalescent care and other important details.

In the event of epidemic, convalescent facilities can be a real problem in improvising units in a hospital not designed for hospital use. It may mean not only equipment, nursing and physical therapy personnel, occupational therapists and volunteers, but providing heating equipment, plumbing, lighting and other facilities in order to make the unit suitable for use.

Administration must be responsible for recreational programs, scout troops, church services as well as other projects to make the child's life as nearly normal as possible, which is all a part of the patient's therapy. If education cannot be provided through local school systems, more recruiting, more expense is part of his job. No administrator should fail to take into consideration the emotional problems of children that go with polio.

The Child Guidance Department becomes a valuable part of polio care.

Almost above anything else, the administrator must understand the problems of parents, both financial and emotional, and when the entire hospital is filled with long-term cases, meetings of parents should become a part of the hospital routine, thus giving an opportunity for these parents to talk to nurses, doctors, therapists and others.

Administrators must recognize their responsibility to their community. Accepting cases is only part of this responsibility. The dispensing of information to press and community organizations must be accurate but should in no sense cause alarm.

The administrator's job covers all phases of polio care, none of which can be ignored; whether it be contacts with staff, patients, parents or the community, this is all part of the everyday duties of the office.

HOME CARE FOR POLIOMYELITIS PATIENTS

EMIL D. W. HAUSER, M.D.

A good home care program provides increased comfort for the patient and further opportunity to recover from the illness and to increase his physical capacity. Good home care is a form of rehabilitation. The greater the restoration of the individual, the less will be the burden on the community; home care for the poliomyelitis patients not only benefits the patient and those near to him but is actually an asset to the community.

Home care for mild cases where complete recovery is possible can often be directed in its entirety by the attending physician with the help of the family alone. It requires specific instructions as to the amount of rest and exercise as well as to the type of exercise until full strength has been re-established. This means keeping the patient under supervision from the time of illness until he is completely restored.

When there is some disability, home care is necessary until the maximum recovery is obtained and the patient can completely take over the adjusted mode of living. Where some disability must be accepted and yet the patient can become entirely self-sustaining, the orthopedic treatment, including physical therapy, casts, braces and surgery must be followed through until the desired effect is accomplished. It includes the responsibility of seeing that sufficient education and occupational training is obtained until the patient reaches the point where he can carry on under his own initiative.

The type of case where disability is great requires home nursing care and home visits from the physical therapist and occupational therapist. Educational activities and medical services will also have to be carried out at home. It is necessary for the medical social worker to establish the amount of expense the family can carry and to make arrangements with the proper social agencies for economic assistance.

The full care of the patient is always the responsibility of the attending physician. He must utilize the community agencies to the best advantage of the patient. The agencies vary somewhat in different sections of the country. My experience has been that the doctor should set his goal high in order to reach the maximum effect.

While the patient is in the hospital a program of care is established and every attempt should be made to carry out an equally beneficial program at home. This includes providing necessary equipment such as hospital beds, overhead frames, hot packing machines, portable respirators and even suction apparatus. A satisfactory diet must be prescribed and also made obtainable. The same is true of any medicine which is deemed beneficial.

The majority of patients are able to attend a treatment center following their discharge from the hospital. More can be accomplished at a rehabilitation center with much less expense than where treatment is given in the individual home. It is economical to have all possible equipment in one place and available to many patients. Where groups of polio patients or other disabled groups work together the morale is high. There is a competitive spirit which urges the patient to maximum effort and there is also a note of cheerfulness and encouragement which is transferred from one patient to another.

A home care program will shorten the period of hospitalization. This is of great economic advantage to the community since home care is much cheaper than hospital care. At the present time the shortage of hospital beds makes early home care desirable. Anything that contributes to the recovery of the patient is of advantage to the community. As soon as the patient returns home a step in the adjustment to normal living has been made. He engages in more functional activities and takes on more responsibility without realizing it. The preliminary physical therapy—muscle training and exercise—carried out in the hospital was to re-establish function. At home the patient carries out these functions in a normal manner. Not only does he develop in strength but he develops in his relationships to other people and in his ability to resume his occupation.

Some type of home care program is essential in providing complete medical care in poliomyelitis. The patients who are severely involved are dependent upon good home care for their very existence. Home care lessens the cost of patient care, thereby decreasing the economic burden of the community.

INDIANA'S POLIO PLANNING COMMITTEE

LEROY E. BURNEY, M.D.

Indiana had its greatest incidence of poliomyelitis in 1949 with 1432 cases. The explosive outbreak began the latter part of July. Representatives from various official and voluntary health agencies directly concerned with all phases of this disease were convened with the following general objectives:

1. To learn of the services each organization had to offer and to secure closer integration and coordination of these services for the purposes of efficiency and economy.
2. To secure general agreement upon policies relative to the management of the disease and the education and guidance of personnel employed to care for the patients involved.
3. To pool existing knowledge concerning the extent of the disease, the need for hospital beds, personnel, equipment and related information.
4. To plan for continuity of care of poliomyelitis patients from the acute stage through convalescence and rehabilitation.

Meetings were held throughout the epidemic. This coordination of planning and action was so successful that the committee was established upon a permanent basis with the additional objective of solving some of the deficiencies discovered during the high incidence of the disease.

The accomplishments of the Planning Committee can be summarized briefly as follows:

Accomplishments of the State Polio Planning Committee

1. A closer integration of all groups, official and voluntary, concerned with the diagnosis, care and control of poliomyelitis.
2. An understanding of the services each group has to offer.
3. An agreement upon uniform policies affecting the poliomyelitis patient and his care and factors relating to him and his community.

4. The establishment by the Indiana University Medical Center of a training course for supervisory nurses consisting of didactic lectures and ward experience.

5. The development of a manual, "Nursing Procedures and Techniques in the Care of Poliomyelitis Patients" for nursing and hospital personnel.

6. The development of a manual containing general information for the public entitled, "General Recommendations for the Control of Poliomyelitis, Including the Services and Facilities of the Various Agencies."

7. The development by the Indiana University Medical Center of a course for the practicing physician on the care and management of poliomyelitis cases, including the responsibilities of the members of the medical profession to their community when poliomyelitis is present.

8. Finally, this Polio Planning Committee has demonstrated that voluntary and official agencies can work together effectively for the best interests of the patient, the community and the state.

THE NATIONAL ASPECTS IN PROVIDING COMPLETE MEDICAL CARE IN POLIOMYELITIS

KENNETH S. LANDAUER, M.D.

The National Foundation for Infantile Paralysis, a public voluntary health organization, supported by the March of Dimes, is committed first to research, to wipe out poliomyelitis, and second to assist in making complete care available to patients. Until a practical preventative against paralytic polio is developed, an end which is hoped may soon be in sight, these efforts must continue.

The National Foundation conducts its patient care and epidemic aid programs through and with doctors, hospitals, health authorities, allied professional groups and health agencies. It owes a great debt of gratitude for the splendid cooperation it receives from all of these. It also owes them a report of its situation.

March of Dimes funds, although increasing annually so far, have not kept pace with the rising costs of care for the pyramiding patient load of recent heavy epidemic years. The N.F.I.P. faces a deficit of approximately $5,000,000 for 1950, and it is imperative that a large reduction in expenditures be effected without sacrificing the amounts or kinds of care actually required to ensure optimum recovery for patients.

Hospital bills are by far the largest item of national expense in our patient care program. Hospital costs now average about $15.00 per patient day. As of August 1, 1950, there were 5,000 polio patients in hospitals; it is estimated that we shall have an average hospital census of over 5,000 polio patients each day for the balance of the year. It is believed that hospital costs can be reduced greatly—with the cooperation of doctors and hospitals—in three major ways:

1. Reduction of hospital admission: Although there has been a real increase in polio in this country in recent years, a disproportionately larger number of acute and suspect patients than ever before are being admitted to hospitals. A number of factors may account for this, among which are (1) many more hospitals accepting acute polio than previously, (2) little or no concern about costs —chapters finance suspects for 10 days, (3) "pest house" attitude of public and many doctors resulting in hospitalization for isolation of patients, (4) publicity of the National Foundation for Infantile Paralysis for "hospitalization for early treatment," (5) physicians' and public's increased awareness of symptoms resulting in more hospital admissions of abortive and nonparalytic cases, (6) fear of development of bulbar or respiratory involvement, (7) admission for spinal taps or observation, when this could often be done at home or in an outpatient diagnostic clinic, (8) referral by many physicians, especially general practitioners, of suspects to hospitals' polio staff care rather than following cases with aid of consultants in the home.

As a result, it is felt that many patients are admitted for hospital care unnecessarily. Those hospitals which use diagnostic admitting clinics find that 20 to 30% of patients sent in during epidemics either have other conditions or do not need hospital care.

Diagnosis and care at home for many acute and suspect patients has been demonstrated to be feasible, safe and far less expensive. Many physicians believe that patients with abortive, nonparalytic or mild polio should be cared for at home when conditions permit because fatigue from transportation in the acute stage appears harmful and psychic trauma from separation and isolation from family, with resultant maladjustments and rejections, are matters for serious consideration.

Physicians are thus urged to cooperate by reducing hospital admissions of those patients who may without serious hazard or prejudice to recovery be as well cared for in the home.

2. Reduction of hospital stay for isolation: It is hoped that the 22 states still requiring prolonged isolation will soon have revised their codes to conform with the recommendations of the National Conference on Recommended Practices for the Control of Poliomyelitis, and with the 26 states now requiring a 7 day isolation period, permit earlier discharge of patients to their homes or to treatment units for after care. This will further reduce unnecessary hospitalization expense.

3. Reduction of hospital stay for physical therapy: Too many physicians turn patients over to physical therapists leaving the patient and therapist without direction or supervision. Overly zealous or inexperienced, medically abandoned therapists often may continue under such circumstances to treat the patient long beyond the need for hospitalization for such treatment and often for long after any further practical benefits may be expected. This is a team work job and a well-planned medically directed program of rehabilitation for each patient with frequent re-evaluation is essential. Physical therapy can often be carried on equally well in the home, or on an outpatient service, with great reduction in costs for hospitalization. Prolonged hospitalization is now necessary for many patients because of lack of physical therapy and orthopedic supervision in or near their homes. The National Foundation has been working for several years to help correct this inadequacy, principally through a professional education program to make more well-trained physical therapists available. Federal appropriations available to state Crippled Children's Services have been increased from $7,500,000 to $12,000,000 this year and to $15,000,000 for next year. These funds should be made use of whenever possible and where needed to improve the follow-up care for polio and other handicapped patients, especially in more rural areas where services and facilities are too often lacking.

Other problems include concern over the increasing numbers of chronic respirator patients, and of other severely and totally disabled patients and the problems of their care. Shortages of epidemic aid personnel, such as doctors, nurses, physical therapists and critical equipment, exist now and threaten to become much more serious. The National Foundation is trying to assist in these problems in every way it can. We believe that with continued cooperative efforts these problems may be solved and we can continue through research to work to the end of all our problems of medical care of polio patients.

Round Table Discussion

LEUKEMIA AND NEUROBLASTOMA

HAROLD DARGEON, M.D., *Chairman,* New York City; JOSEPH H. BURCHENAL,* M.D., New York City

CLAYTON T. J. DODGE, M.D., East Cleveland, and ERNEST R. KIMBALL, JR., Evanston, Ill., *Secretaries*

TREATMENT OF ACUTE LEUKEMIA IN CHILDREN†

Dr. Burchenal: The 2 types of compounds most useful in the treatment of acute leukemia are the antimetabolites of which amethopterin and aminopterin are examples, and the hormones such as ACTH and cortisone. Today I would like to discuss with you the indications, dosage, undesirable side effects, and results to be expected with these 2 types of therapy.

If the child with acute leukemia is in reasonably good shape, if his total leukocyte count is below 50,000, and it appears that he will probably survive at least 3 to 4 weeks even without treatment, we start him on amethopterin because we feel that the survival times of patients treated successfully by this method are superior. On the other hand, if his WBC is above 50,000, or he looks as if he would not last long enough to have an adequate course of amethopterin, then we start with ACTH or cortisone, and shift to amethopterin when the WBC has returned to more normal levels, and the general condition has improved.

It should be emphasized at this point that good clinical and hematologic remission can be achieved initially in only 30 to 50% of patients treated with amethopterin, and in only 40 to 60% with the steroid hormones. Fortunately a case that does not respond to one type may respond to the other. In addition, patients who have derived several remissions from courses of amethopterin and have finally become refractory to this type of therapy will frequently still respond to the steroids, and vice versa. In such cases, we then return to amethopterin when the inevitable relapse occurs after cortisone or ACTH. In an occasional patient there is a temporary loss of amethopterin-fastness and 1 or 2 more remissions from this drug may be obtained.

TABLE 1

Drug	Dosage (mg.)	Preferred Route	Frequency
Aminopterin	0.5–1.0	P.O.	Daily
Amethopterin	2.5–5.0	P.O.	Daily
ACTH	15–25	I.M.	Every 6 hr.
Cortisone	25–50	P.O.	Every 6 hr.
Cortisone	100–150	I.M.	Daily*

* Dose may be divided if desired.

The amounts of aminopterin or amethopterin that patients need to produce remissions, or can tolerate before developing symptoms of toxicity (stomatitis, diarrhea, gastrointestinal bleeding) vary tremendously and it is to be emphasized that dosage must be suited to the individual patient. Particular care must be exercised in the administration of these drugs to severely debilitated patients, or to those with impaired renal or hepatic function. Leukemics with initial high peripheral leukocyte counts may also be extremely sensitive to antagonist therapy. The usual daily dose of these drugs in a 5 year old child would be 0.5 mg. to 1 mg. of aminopterin, or 2.5 mg. to 5 mg. of amethopterin by mouth in tablet form. Although the intramuscular administration may also be used if desired, there

From the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 16, 1950.

* Damon Runyon Senior Clinical Research Fellow.

† From the Chemotherapy Service of Memorial Hospital, New York City.

seems to be no advantage to this route. During therapy, daily determinations of hemaglobin, white blood count and differential counts should be done.

The plan of therapy used here in the treatment of some 97 children with acute leukemia calls for administration of the drug until either a complete remission occurs as evidenced by clinical signs and by the blood and marrow differentials, or until toxic manifestations of stomatitis, diarrhea or gastrointestinal bleeding appear. In the patient showing signs of toxicity, if a complete remission does not occur, therapy is resumed at a slightly lower dose in 1 or 2 weeks when the symptoms have subsided, and is continued until the signs of remission or of further toxicity appear. The first signs of remission are usually seen within from 14 to 35 days after the start of therapy, but wide variation in the time of response may occur.

Once a complete remission has been produced, maintenance therapy may be given or treatment may be temporarily stopped. We prefer the latter course. The patient is followed by means of clinic visits every 2 weeks, at which time a short interval history for symptoms of toxicity, a careful physical examination, and determination of hemoglobin, white blood count, peripheral blood and marrow differentials are done. Particular emphasis is laid on the sternal aspiration in the intermittent type of therapy as it is usually by this technic that the first evidence of relapse can be detected. Thus the treatment can be resumed and the relapse aborted, often without clinical evidence of a relapse ever appearing.

It is our experience that in some of the cases of acute leukemia which respond to therapy, a definite diagnosis of myeloblastic or lymphoblastic type can be made, but most of the cases which respond can only be designated as stem cell leukemia. The acute monocytic type does not usually respond. In those patients who have responded once, repeated remission can be expected. Eventually these responses become less and less satisfactory and finally the patient becomes resistant to therapy.

ACTH or cortisone administered in the dosage given in table 1 will bring about an initial remission in 40 to 60% of the cases. Often within 48 hours with ACTH or 5 days with cortisone there is a marked increase in appetite and feeling of well being. The first signs of an impending remission are usually an increase in the reticulocyte counts, and an increase in the percentage of erythroid elements in the marrow with a concomitant decrease in the leukemic cells. Complete remissions lasting 1 to 12 weeks may be achieved after from 10 day to 6 weeks of therapy.

When this occurs, therapy is discontinued and only restarted when there is marrow evidence of a relapse. Second remissions are fairly frequent in children, but may require higher dosage. Third remissions with these drugs, however, are rare in our experience.

The undesirable side effects of such therapy are those commonly associated with overactivity of the adrenal cortex. Sodium retention with consequent edema may be largely prevented by the use of a low salt diet. Hypokalemia may be corrected, if it does occur, by the oral administration of potassium chloride. The undue gain in weight following the increase in appetite may be largely avoided by limiting the diet to that considered adequate for a normal child of that size and age. Other side effects are not so easily controlled, and severe hypertension, with or without hypertensive encephalopathy, and the appearance of psychic disturbances, are indications for withholding therapy. Cushing's facies, acne and hirsutism are not usually of sufficient importance to contraindicate further treatment, and gradually disappear when therapy is discontinued. Severe overwhelming infections not responding promptly to vigorous use of antibiotics are occasionally seen after prolonged therapy with ACTH and cortisone. Whether these are the results of a relatively fixed output of steroids and an inability of the adrenal to respond to the stress of infection is not understood clearly at present. It may be that in such situations massive doses of cortisone by mouth will be of value.

By these technics of therapy it appears that a definite prolongation of life may be achieved in many cases. In those patients responding initially to amethopterin an average survival of over 16 months from the start of the disease, and over 14 months after the start of treatment may be expected. In those treated initially with the steroids the results are somewhat less satisfactory. By these methods it is possible to keep some children alive, and in reasonably good health, from 18 to 27 months from the onset of their disease, in the hope that they may survive long enough to benefit from new discoveries in the field of chemotherapy.

DIAGNOSIS OF NEUROBLASTOMA*

Dr. Dargeon: The diagnostic difficulties encountered during the early course of many tumors of childhood are familiar to all pediatricians. The multiplicity and variability of the early symptoms

* From the Pediatric Service, Memorial Center for Cancer and Allied Diseases.

and signs of well known tumors such as those of lymphoid origin and those of the central nervous system are paralleled in the case of neuroblastoma.

A survey of 58 cases of this neoplasm in children at Memorial Hospital has been made and the data obtained pertaining to color, age, sex, previous health, racial origin, family history of cancer, initial evidence of disease, delay in diagnosis and period of survival is presented in chart 1.

CHART 1

NEUROBLASTOMA IN CHILDREN

58 Cases

Age on Adm.	Color	Sex	Nationality	Previous Health	Family Hist. Ca.	1st Sympt.	1st Sympt. to Therapy	Survivors
1 yr./6	White/58	M/29	American/23	Good/41	Positive/22	Mass/34	under 1 mo./10	over 5 yr./3
1–4 yr./31		F/29	Other/20	Poor/7	Negative/30	Pain/12	1–5 mo./31	over 4 yr./2
5–9 yr./18			Unknown/15	Unknown/10	Unknown/6	Fever/3	6–10 mo./6	1–4 yr./4
10–14 yr./3						CNS/5	11–15 mo./4	
						Pallor/1	over 15 mo./2	
						Wt. loss/1	doubtful/5	
						GI/2		

The diagnosis is sought by history and physical examination, roentgenographic examination, marrow studies and biopsy. Study of the tissue obtained from biopsy by tissue culture, chick embryo culture in addition to histologic examination may be helpful in identifying the nature of the tumor.

History and Physical Examination

Reference to the chart indicates that the initial findings vary so considerably that no specific symptoms should be expected and that therefore the disease should be included in the differential diagnosis of a multitude of clinical syndromes—those with tumors of the head, neck, thorax, abdomen, back or extremities, fevers of obscure origin; motor or sensory disturbances, chronic and acute abdominal symptoms, adenopathies and osseous disorders.

Roentgenography

The sites which should be examined are the thorax, the abdomen and the skeleton:

1. Thorax: In common with other thoracic neurogenic tumors the neuroblastoma arises most frequently in the posterior mediastinum.

2. Abdomen: The shadows cast by abdominal neuroblastoma are partially radio opaque and may contain calcified areas within them. Certain tumors may displace adjacent viscera or supporting structures and alter the normal configurations of the diaphragm, psoas muscles and kidneys.

3. Skeleton: Involvement of either cancellous or long bones is manifested usually by multiple small irregularly outlined osteolytic lesions. There may be periosteal reaction and the long bones show the disease in any portion of their shafts.

Marrow

The usual hematopoetic cells are diminished in number or at times completely replaced by the comparatively large neuroblasts.

Biopsy

Histology: The tumor is very cellular. The stroma is not abundant. The cells are usually arranged in rosettes but may occur in clusters. The cytoplasm is often indistinct, the nuclei stain densely. Neurofibrils may be identified by special stain. Tissue culture and chick embryo transplants will frequently produce growth of cells with neurites.

Differential Diagnosis

In considering the differential diagnosis it is known that the causes of many of the symptoms may be nonneoplastic in origin and therefore include congenital malformation, infection, metabolic defects and hyperplasias. Examples of some cases which presented differential diagnostic problems are shown: osseous tuberculosis, fibrous dysplasia, reticuloendotheliosis, reticulum cell lymphosarcoma, leukemia,

Wilms' tumor, teratoma, Hodgkin's disease, ganglioneuroma and congenital malformation of the heart.

Finally there have been frequent enough variations in the usual course of the disease in this series to suggest that we may be compelled to modify our present opinion of what constitutes the "typical case" of neuroblastoma when satisfactory data have been studied on a sufficiently large number of cases. The following cases illustrate variations from the usual as to primary site, progression, metastasis and result.

Case 1. A boy of 3 years who has 2 types of neurogenic tumor, neuroblastoma and ganglioneuroma.

Case 2. A boy of 4 years who had a slowly growing, inoperable retroperitoneal neuroblastoma. He was followed over 2 years and the tumor did not metastasize. Death resulted from hemorrhage within the tumor.

Case 3. A male baby of 5 months with a primary tumor arising from the cervical sympathetic. This was noticed 2 days after birth.

Case 4. A male baby of 8 months with multiple cutaneous and subcutaneous lesions 0.3 to 3 cm. in diameter, axillary lymphadenopathy and no other evidence of disease. He has survived 14 years.

Case 6. A girl aged 14 months who had an extradural neuroblastoma extending from T-6 to T-9 which produced motor disturbance of the legs. Subsequent to laminectomy and irradiation evidence of disease was observed in her lungs. She has survived 2 years. There is evidence of intrathoracic extension of her disease.

Case 7. A female infant, 14 months of age, with metastasis in the cervical region from a primary intrathoracic tumor. This patient has no evidence of disease 5 years after treatment by irradiation only.

Conclusion

Neuroblastoma in common with many other tumors of the juvenile age period presents a diagnostic challenge to the clinician. The conditions should be included in the differential diagnosis of many acute and chronic syndromes in early childhood whether or not a tumor is clinically evident. The possibilities of a favorable result are not always determined solely by an early diagnosis but the prognosis in the occasional case of neuroblastoma may be favorably influenced by early recognition of the disease.

Pediatrics

VOLUME 8 NOVEMBER 1951 NUMBER 5

SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

COMMUNICATION FROM ARNOLD GESELL, M.D.

DEAR DR. HARPER:

The excellent statement of the American Board of Pediatrics in the March issue of PEDIATRICS has stirred me to communicate with your editorial department.

In 1935 the American Board of Pediatrics set up the field of Growth and Development as a basic requirement for specialty certification. That this was a far-seeing action is testified by the challenging official statement of the Board which was printed in the March 1951 issue of PEDIATRICS (The Pediatrician and the Public, pp. 430-432).

This statement is so constructive in essence and so liberal in tone that it is sure to attract wide acceptance. The statement, however, deserves more than acquiescence and should initiate new undertakings to meet the training requirements so clearly indicated. The Board does not assume the task of outlining specific training programs. The possibilities are so diversified that it would be desirable to have various training centers, devoted to special aspects of infant and child development. If the approach is soundly developmental, the danger of overspecialization is small; because development is an inclusive, integrative concept which embraces the "total health." The concept applies with equal force to the well child and to the handicapped. It applies equally and conjointly to physical and to mental health. In fact, health can now be defined as that condition which permits and promotes optimal development.

These considerations must govern any adequate training program. The clinical implications are far-reaching. The Board has stated them generally in this sentence: "There can be little doubt that evaluation of candidates for proficiency in health supervision of infants and children is best ascertainable by assessing the adequacy of their information in the field of growth and development." How can this information be best supplied?

Undergraduate training can anticipate later needs. This may be done not so much through revisions of the medical curriculum, as through methods of teaching which will

demonstrate developmental mechanisms and age factors whenever the subject matter permits. A developmental approach does not encumber factual knowledge, but tends to clarify and simplify. Anatomy moves from a descriptive to a dynamic level when studied from the standpoint of growth and development.

Embryology is pre-eminently the science of development. Frequently it is taught in a supplementary and incidental manner with emphasis on prenatal cross-sectional morphology. Embryology could become a key discipline for imparting a knowledge of growth as a process—a process which produces functional as well as physical forms.

The terms growth and development do not need separate definition, for they are actually interchangeable. But it is important for the medical student to realize that the mechanisms of embryology embrace postnatal as well as prenatal growth and apply equally to the developmental anatomy, the physiology, and the behavior of fetus, infant, and child.

Such a conceptual orientation is basic for the developmental type of health supervision which the Board of Pediatrics evidently seeks to strengthen. The student needs to acquire a developmental point of view as well as a body of factual knowledge concerning the norms and symptoms of human growth. This developmental outlook can be fostered not only through the study of a broadened embryology, but incidentally to numerous areas of preclinical and clinical instruction. Didactic teaching alone, however, will not suffice. Facts are not likely to be incorporated into later practice unless there is a genuine awareness of the lawful nature of the growth process as embodied and observed in actual children, normal and abnormal.

In this sense the prospective practitioner needs above all to be imbued with the philosophy of a developmental approach to the manifold problems of health supervisions. A brief general introduction to the principles and laws of child development is well within the scope of the basic training of the medical student.

At the interne and resident levels, however, "pediatric centers must increasingly assume the responsibility for the day to day teaching of growth and development in a clinical setting."

The Board goes on to state, "We are interested primarily in providing the prospective pediatrician with tools for the most optimal practice. This means the teaching of physical mental, emotional, and social growth in their interrelationship since one of the most important functions of the pediatrician is the guidance of the total growth, development, and ultimately social adjustment of the individual." Such day-to-day teaching will not overstress any single phase of child development but it will inevitably focus upon the diagnosis and supervision of behavior characteristics. Behavior is the most comprehensive index of developmental status and of developmental potentials.

Developmental diagnosis utilizes clinical norms and functional tests of behavior to define the maturity and integrity of the action system of infant and child.

Developmental supervision and guidance must naturally rest upon sound diagnosis and repeated appraisals of the child in his family setting. This is the province of developmental pediatrics as a form of clinical medicine.

It follows that the basic requirement for training in developmental pediatrics must be experience in the actual diagnosis and supervising appraisal of infant and child behavior. This should mean that a separate locus is set aside by the training center, with special though simple equipment, for conducting formalized examinations of infants and young children, normal and deviant, referred or selected for developmental diagnosis. The practicability of the teaching arrangements I am about to outline has been demonstrated on

the diagnostic and advisory service of the former Clinic of Child Development at the Yale University School of Medicine.

Like any other technique of clinical medicine, developmental diagnosis may be undertaken at various levels of skill and thoroughness. As a clinical specialty it demands at least a year of postgraduate preceptorship training in addition to a basic internship in general pediatrics or neuropsychiatry. Needless to say an increasing number of qualified developmental specialists is needed to implement training programs in the field of child growth and development. It is not assumed that the general pediatrician aspires to be in addition an expert clinical psychologist or an analytic psychiatrist. He can, however, acquire a working familiarity with basic behavior examination procedures, and a developmental insight into the symptoms of behavior deviations. He does not hesitate to make a limited neurological or orthopedic examination when the situation so demands. He need not hesitate to make a few standardized behavior tests which may give evidence as to the maturity, and the organization of the underlying action system. He can not rely on incidental impressions and interviews alone, nor on intuitive speculation as to hidden psychological forces.

A pediatric examination of behavior is a strategic tool for detecting sensori-motor handicaps, and personality deviations; because it is in essence a series of functional tests with established normal criteria. The tests are relatively simple, but they are administered with clinical discernment as part of a normal life situation, designed to put the infant at his best. With this approach, which demands a careful regard for the child's individuality, even a brief examination serves to define areas for guidance; and for comparative follow-up appraisal on the next examination. The entire test situation, in conjunction with pertinent history and correlated observations of the parent-child relationship, affords a diagnostic basis for a personalized developmental supervision of a growing infant in a family situation. From the standpoint of prevention and guidance, such pediatric supervision is pre-eminently indicated for the first three or five years of life. The methods of developmental study and supervision are fundamentally the same for normal, atypical, defective, and specifically handicapped children. They apply to everyday behavior problems. A developmental approach is extremely important in the more permanent handicaps, because the parents feel peculiarly alone and lost if they do not have periodic recourse to the physician's re-examination and advice. In all complicated cases, involving physical growth factors, long range therapies, and group diagnosis, consecutive developmental behavior records have especial value. But the basic methods, procedures, and applications of developmental diagnosis are most significantly demonstrated with the well, normal infants who consume over half of the pediatrician's time. A well baby conference provides an excellent clinical setting for the implementation of a systematic training program; because the diagnostic principles and procedures are rooted in the lawful processes of normal development.

This communication has attempted to stress the clinical significance of the concept of growth, with special emphasis on the principles and avenues of diagnosis. Although the life sciences are currently making important advances in the study of growth and development, there is no single codified body of knowledge ready for application. In time it may prove desirable to define the minimum essentials of a policy of developmental supervision of infancy and early childhood. The social pressure for a broadened pediatric extension of health supervision is mounting and it embraces the entire infant and child population.

The task is tremendous; the Board at present naturally finds it wise not to prescribe a stereotyped teaching program.

It is possible, however, to suggest a list of feasible teaching objectives. The following are summarized in tabular form for the sake of brevity and concreteness:

1. Command of a graphic method of recording physical growth, supplemented by entries on body type, nutritional, and physiological factors bearing on individual growth patterns.

2. Interview items and methods for securing a significant developmental history, with reference to family situations as well as child adjustment.

3. A working knowledge of salient developmental sequences in the major fields of behavior, including social and emotional adjustments to child care. Special emphasis on the first year of life and the preschool years.

4. A detailed familiarity with the physical and behavioral characteristics of a few selected maturity levels. These maturity characterizations of a total normative child to be used as reference tools for clinical orientation and interpretation.

5. Abundant observation of normal infants and children, with participation in conferences on individual differences and clinical deviations. Intensive periodic study of a few specimen cases to illustrate the problems of continuing care, and to invite skill in parent-physician relationships.

6. Actual developmental examinations of normal infant behavior at selected ages. The purposes of these examinations are several:

   a. To demonstrate to the examiner himself the validity of behavior patterns as significant indices of maturity.
   b. To show that he himself can elicit these patterns and put the technique to elementary clinical use in his practice.
   c. To impart a more vivid and vital sense of the growth process when brought under periodic, objective scrutiny.
   d. To encourage him to self training in a field of diagnosis, which he must enter if the total health and development of the child come under his responsible care.

If such and related objectives are to be realized, we must look to the leadership of pediatric centers as well as to the initiative of individual internes, residents and practitioners. The demands for a developmental type of pediatrics are rising in volume and penetration. The American Board of Pediatrics has issued a timely challenge.

ARNOLD GESELL, M.D.
New Haven, Conn.

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

FINANCIAL SUPPORT FOR PEDIATRIC RESEARCH*

MORE than a year ago a new move to provide urgently needed support for effective pediatric research was inaugurated with the founding of the Playtex Park Research Institute by the International Latex Corporation, of Dover, Delaware. The Institute was founded by its sponsor as a nonprofit foundation devoted to supporting investigations in the field of child health. In bringing the Institute into being it was agreed that its funds were to be used, not for buildings and equipment, but for "the facilitation and coordination of scientific research concerning the nature, prevention, causes, treatment and cure of diseases and disorders, and the factors responsible for normal growth and development in the infant." It was further stated at that time that the Institute's support of research would be based on the ability and promise of the investigator, rather than only on the field of investigation.

The Academy's Study of Child Health Services showed that in 61 out of 67 medical schools reporting, the portion of the school budget allotted for pediatric departments ranged from less than 2% to only 6%. In only six schools was an appropriation of 6% or more allotted to the pediatric department, with a high of only 8% in the latter group. Out of the 22 schools where this department received less than 2% of the total school budget, eight received no outside support and two received less than $1,000 from outside sources. These startling facts were among many which prompted the International Latex Corporation to establish and finance the Playtex Park Research Institute.

That the need for support of pediatric research and education was not transitory but is still with us and is increasing in urgency, is revealed in the 51st Annual Report on Medical Education in the United States and Canada by the Council on Medical Education and Hospitals of the American Medical Association. This report† shows that pediatric departments lead the list of clinical departments in medical and basic science schools of the United States in the number of unfilled full time positions for the period 1951-1952. The number of such unfilled positions was greater than was reported the year before.

Platex Park Research Institute, which is endeavoring to fill some of the needs pointed out in the foregoing, is operated by a board of 18 nationally recognized leaders in pediatrics who serve without remuneration and who are solely responsible for the administra-

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* This article is approved by the Executive Committee of the Board of Governors of Playtex Park Research Institute:

Sidney Farber, M.D., Chairman
W. O. Heinze, Treasurer
Charles F. McKhann, M.D.
Joseph Stokes, Jr., M.D.
Lawrence C. Salter, Secretary

† J.A.M.A. 147:131, Sept. 8, 1951.

tion and allocation of funds for the Institute. The Institute's Board of Governors is composed of the following:

Katherine Bain, M.D., Associate Chief for Program Development, Children's Bureau, Federal Security Agency

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Myron E. Wegman, M.D., Professor of Pediatrics, Louisiana State University School of Medicine

James L. Wilson, M.D., Professor of Pediatrics, University of Michigan Medical School

The first grants by the Institute were made by the Board in 1950. There were 12 individual grants ranging from $5,000 to $24,000 each. All but one of the grants were for three years. In 1951 the Board made commitments for 15 additional grants ranging from $5,000 to $18,000 each, the majority of which similarly are for three years' duration. The grants are for the support of investigators in the field of pediatrics, many of whom, without the additional support provided by the Institute, would be lost to pediatric research because of the budget limitations of the institutions with which they are affiliated.

Among grants which have been made by the Institute are the following:

Chemotherapy of mental retardation, Cleveland (Ohio) Heart Society

Hormone factors in water and electrolyte metabolism in premature infants, Columbia University College of Physicians and Surgeons, New York

Growth promoting factors related to kidney function, Children's Hospital, Philadelphia

The relationship of adrenal hormones to aromatic amino acid metabolism in premature babies, Cornell University Medical College, New York

The anterior pituitary growth factor, Cornell University Medical College

A study of uterine contraction throughout pregnancy with particular reference to uterine motility in pregnancies which come to term and those which end prematurely, University of Colorado, Denver

Studies on the passage of proteins through living membranes, New York Medical College

Adrenal hormones and infection, Louisiana State University, New Orleans

Hormonal control of water and electrolyte balance in premature infants and comparative studies in older infants and children, Columbia University College of Physicians and Surgeons

The role of emotional factors in the causation, precipitation and perpetration of disease, Yale University, New Haven, Conn.

Amino acid metabolism with particular reference to the influence of adrenal and adrenotrophic hormones, New York University College of Medicine

Physiological basis of diarrhea in infancy, University of Michigan, Ann Arbor

Kidney function in young infants, Cornell University Medical College

Physiology of endocrine abnormalities, Massachusetts General Hospital, Boston

The identification of factors concerned with the growth of bone, Children's Hospital, Boston

A new approach to the problem of increasing the blood supply to the kidneys and to the liver by means of arterial shunts and/or grafts, Montefiore Hospital, New York

A study of the abnormal metabolic processes concerned in the development of the leukemic state in infants and children, University of Illinois College of Medicine, Chicago

Most of these are studies of fundamental value in attacking disease and death in the vulnerable years of infancy—an age group in which mortality rates are higher than any period until the age of advanced years.

It will be noted that the grants made by the Board not only cover many fields of investigation in pediatrics but are also widely distributed geographically. It is the feeling of the Board that one of its objectives should be the support of men of promise throughout the country rather than concentrating on a few medical research centers.

The Board believes that the soundness of its selection of grants is evidenced by the number of papers which are beginning to appear in medical literature and on the programs of various scientific medical bodies, and which are giving credit to Playtex Park Research Institute for making those studies possible. Several of the grants already have made significant contributions to our knowledge of pediatrics.

In a little more than a year the founder and sponsor of the Institute, the International Latex Corporation, has made commitments to it of more than one-half million dollars. It is felt that the sponsor is to be congratulated on its acceptance and generous support of a civic responsibility as it saw it.

The success of the Institute to date does well to serve as an example of effective teamwork of industry and medicine and it is hoped that this will inspire other companies to emulation.

SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

NEUROTROPIC VIRUS DISEASES

With Special Reference to Natural Immunity and Artificial Immunization in Poliomyelitis

By W. McD. HAMMON, M.D., Dr.P.H.
Pittsburgh

AMONG a large group of neurotropic viral infections of man, poliomyelitis is currently of greatest importance to pediatricians of most countries. In all areas of the temperate and tropical zones where surveys have been made, poliomyelitis infection rates, as measured by the neutralization test, are approximately the same as those for rubeola or other common acute infectious diseases of childhood. In many countries the fatal and paralytic cases assume considerable importance in pediatric practice and, above all, in public interest and demand for control. In many tropical and subtropical areas, however, paralytic rates are reputedly low, and this disease is not recognized as a problem of any importance.

In some areas of the world other neurotropic viruses assume an importance equal to or greater than that of poliomyelitis. Epidemics of these other viruses may occur at intervals as frequent as those of poliomyelitis epidemics or at longer or shorter intervals, but when epidemics do occur they are occasionally of major proportions. Outbreaks of Japanese B encephalitis have occurred principally in children in the past 15 years in Japan, Okinawa and certain other Far Eastern areas. Western equine encephalitis virus has been responsible for important outbreaks in children in the central valley areas of California, and the St. Louis virus has also been responsible for local outbreaks involving principally children in the western United States. These viruses are all members of the arthropod-borne group of viral encephalitides.

Epidemic parotitis, although not usually listed among the neurotropic viruses, has come to occupy a more and more important position as the serologic tests for its diagnosis have received more widespread use in the diagnosis of cases of the nonbacterial meningoencephalitides. In the author's experience and that of many other American workers, mumps virus has been demonstrated to be a significant cause of encephalitis in children and adults who have no detectable parotitis or other salivary gland involvement.

In recent years a group of neurotropic viruses known as Columbia SK, M.M., Encephalo-myocarditis and Mengo have received considerable attention, and some have considered them as reasonable members of the poliomyelitis group. They have now all been shown to be immunologically identical[1, 2] but not related immunologically to any poliomyelitis virus. The normal human pathogenicity of this group is still unevaluated and much remains to be known of their epidemiology, although rats and other rodents are a probable reservoir.[3]

From the Department of Epidemiology and Microbiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh.

Aided by a grant from The National Foundation for Infantile Paralysis, Inc.

Read at the Sixth International Congress of Pediatrics, Zurich, Switzerland, July 1950.

(Received for publication Aug. 6, 1951.)

There are a large number of other viruses attacking the central nervous system including rabies and lymphocytic choriomeningitis, but since all of these are seen only rarely in pediatric practice or belong in a group as yet inadequately studied, they will not be dealt with in this discussion. The remainder of this paper will deal with certain of the newer developments in poliomyelitis research which may lead to methods of control.

One of the most interesting facets of poliomyelitis, which has been receiving much attention in recent years, is an apparent change in the age distribution of the reported disease. This has been pointed out as occurring in a number of countries. The older age distribution has been considered as due to a postponement of the age of infection.

The best measurement of the incidence of infection is obtained by applying the neutralization test to a representative series of blood sera from a large range of age groups. Apparently, any commonly occurring immunologic type of virus may be used, but a mouse-adapted strain[4] is most practical. However, to make a comparison of what occurred in one area 30 years ago to what is occurring now is hardly possible. It has been possible, however, to apply the neutralization test to an area where poliomyelitis age distribution is low at present, as it was many years ago in certain cities in the United States, and simultaneously to sample a population where the age distribution is now high. Table 1

TABLE 1

AGE DISTRIBUTION OF LANSING POLIOMYELITIS NEUTRALIZING ANTIBODIES AND MODAL AGE OF REPORTED CASES IN 4 AREAS

Area	Modal Age Reported Cases	Age Group, Sera Tested, and Per Cent with Antibodies										Total No. Sera Tested
		1–3		4–6		7–9		10–12		13–15		
		No. Tested	%+	No. Tested	%+	No. Tested	%+	No. Tested	%+	No. Tested	%+	
Guam	No cases*	36	79	24	88	21	95	10	80	11	100	102
Mexico City	1†	29	69	15	87	12	92	22	100	—	—	78
Bakersfield, Calif.	3‡	65	25	98	36	111	71	13	92	13	77	300
San Francisco	5–9§	11	18	56	59	120	43	118	53	96	63	401

* Personal investigation, official records and correspondence.

† Official reports.

‡ Our own data for both paralytic and nonparalytic cases, as observed 1944–1947.

§ Data obtained from files of California State Department of Public Health.

presents the results of such a study which we made in Guam where no cases are recognized, in Mexico City where the age distribution of reported cases is currently low, in Bakersfield, Calif., where it is somewhat higher and in San Francisco, Calif., where it is still higher. It will be noted that the infection rate as indicated by the per cent with antibodies at different ages correlates well with the reported age distribution of cases. Illustration of this might be multiplied with examples from our work and that of a number of others. We are probably justified, therefore, in reasoning that an increase in age distribution of cases means a retarded spread of virus in the community.

Since changes in age distribution like these have occurred with the passage of time in the same community, some factor or factors in the trend of modern civilization have apparently reduced the rate of transmission of the virus.

TABLE 2

PER CENT OF GUAMANIAN CHILDREN, BY AGE WITH LANSING POLIOMYELITIS ANTIBODIES

Age	No. of Sera Tested	Per Cent Positive
1	14	57
2	10	90
3	12	100
4–6	24	88
7–9	21	95
10–12	10	80
13–15	11	100
Total	102	

It has also been postulated or claimed that a paradox has occurred in this age-infection rate trend. With the reduced rate of transmission leading to an older average age of cases, it is stated that the morbidity rates for the clinically diagnosed infections have also increased; less infection, more disease—a true paradox. To establish this latter point (increased morbidity) is extremely difficult for it depends upon completeness and accuracy of reporting. In poliomyelitis, as in other diseases, reporting is usually entirely inadequate and the tendency to report nonparalyzed cases is increasing. This makes comparison of morbidity reports from previous years a very unreliable procedure. However, although there is some indication from falling death rates and other data that no upward change in morbidity rates has actually occurred in certain parts of the United States in the last 30 or 40 years,[5,6] there is, nevertheless, good evidence pointing to the fact that where there are high infection rates in the very young, the clinical disease rate may be extremely low. No paralytic poliomyelitis has been noted among native Guamanians[7] since the large epidemic of 1899,[8] although they have had careful medical supervision by the American Navy for many years. Yet, we found antibody developed at an earlier age among Guamanians than in any other area sufficiently studied (table 2[7,9]). From recent careful inquiries made in Mexico, we are quite adequately convinced that poliomyelitis has just begun to

TABLE 3

REPORTED CASES AND DEATHS DUE TO POLIOMYELITIS IN FEDERAL DISTRICT AND WHOLE OF MEXICO, 1940 TO 1949

Year	Federal District of Mexico		Mexico Total	
	Deaths	Cases	Deaths	Cases
1940	6	13	22	91
1941	5	6	25	34
1942	4	8	23	43
1943	6	9	22	61
1944	10	31	47	73
1945	6	13	29	68
1946	23	122	111	247
1947	11	115	54	216
1948	37	169	169	653
1949				683

assume an epidemic pattern in a few urban areas and that morbidity rates were previously at a lower level and less periodic. Reported cases and deaths, 1940 to 1949, are shown in table 3. Present trends in 1950 are at about the level of 1949. It would appear safe to postulate that infection in these cities is now somewhat more delayed than previously and that this results in an accumulation of susceptibles in the age group over 1 or 2 years and that this permits small epidemics with an increased total morbidity. One wonders whether this trend will continue until it assumes the pattern observed in the United States.

To draw such conclusions requires one assumption—that infection at an early age seldom results in a disease diagnosed as poliomyelitis and that susceptibility to paralysis increases with age. It will be recalled (table 1) that over 50% of the infants on Guam are infected before the first birthday and paralytic disease is not observed there. However, according to a very complete report made by a visiting American naval medical officer in 1900,[8] a disease fitting closely the clinical syndrome of paralytic poliomyelitis attacked a large portion of that isolated population, but paralytic cases occurred chiefly in the age groups above 15 years and spared the very young. We might postulate that since that apparent introduction of virus by a trading ship it has spread rapidly during infancy, and the population has remained free from paralytic disease through early immunization.

A recent report from Chesterfield Inlet in Hudson Bay, Labrador, confirms this observation.[10] Here, however, strains of virus were isolated, proving the disease to be poliomyelitis.[11] Extremely high morbidity rates occurred and infants and small children were almost completely spared (table 4).

On the basis of these data the paradox of retarded virus spread resulting in increased morbidity rates does not appear so untenable.

Establishing more definitely that infection in infancy is comparatively free from danger of paralysis and, of equal importance, that no other dangerous form of the disease at that age goes unrecognized now, might lead to some practical control measures through induced infection at that very early age. Determining the cause of apparent resistance at this age might lead to means to control of the disease in older children. Dr. G. M.

TABLE 4

CASES AND AGE SPECIFIC RATES PER 100,000 POPULATION OF POLIOMYELITIS BY AGE GROUPS IN DISTRICT OF CHESTERFIELD INLET, HUDSON BAY, 1948–1949*

Age Group	Cases	Rate/100,000
0–4	2	4,000
5–9	13	23,000
10–14	8	25,000
15–19	11	42,000
20–24	4	22,000
25–29	2	16,000
30–34	6	25,000
35–39	1	11,000
40–44	2	20,000
45–49	3	33,000
50–54	0	0
55–59	2	25,000
60–	3	23,000

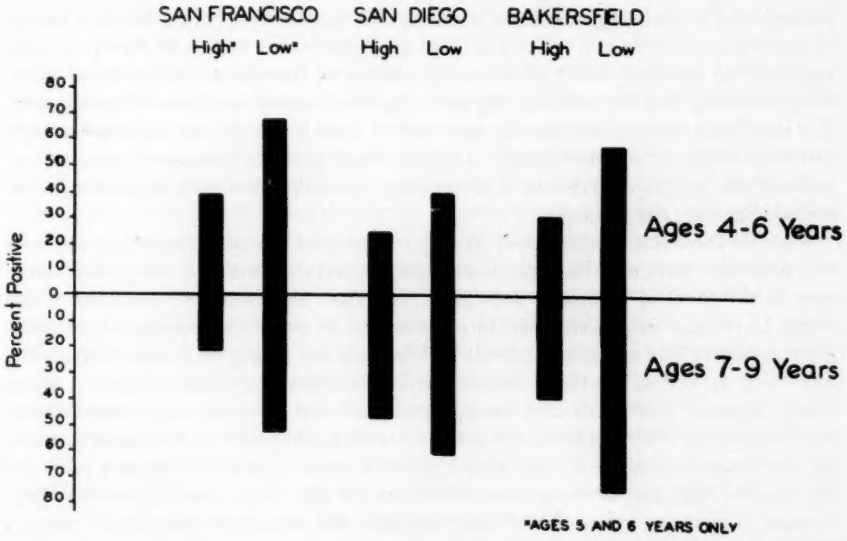
* Peart.[10]

Findlay pointed out in discussion of this problem last year at the International Congress of Neurology in Paris that children were fed much longer at the breast in those countries where poliomyelitis morbidity rates were low. He suggested the possibility of an agent in mother's milk which offered passive protection during the period when infection was usually acquired. Following this, Dr. Sabin began some tests with breast milk that he reported on recently. He has found some protection for mice by using human milk.[12]

In a search to determine one or more contributing factors to the delay in poliomyelitis

CHART 1

PERCENT OF NORMAL CHILDREN WITH ANTIBODIES TO POLIOMYELITIS IN THREE CITIES BY ECONOMIC GROUP AND BY AGE GROUP



virus spread, the author and coworkers have been making large serologic surveys of the high and low economic groups in each of several different geographic areas. Chart 1[9] shows that in each of three California cities infection occurs significantly later in the upper economic group than in the lower. In each of these cities both groups drank from the same water supply and in two were serviced by the same types of inside flush toilets and sewage systems. These children, of course, also lived under similar climatic conditions. Other factors related to economic status, therefore, must have played a role in influencing infection rates.

In examining family sizes[9] it was found that the children selected from the lower economic groups came from larger families. Furthermore, within each economic group, family size correlated with age of developing infection. It seems quite logical that the large

family offers greater opportunity for one member to bring infection to the family from an outside contact. There is much evidence to point to poliomyelitis spreading readily to most members in a family, once introduced. An intimate type of family contact appears to facilitate spread and probably accounts for most cases.

It is common knowledge that family size has decreased with the advance of "civilization" and, furthermore, modern trends of living have reduced the custom of families of near relatives living close together in villages or in a neighborhood where frequent intimate visiting of large numbers of related children and adults occurs more or less as if they were one family under one roof. Much more family privacy now exists—a type of family isolationism. This may account for much of the difference noted in the rate of virus spread between Guam, Mexico City and the upper economic group in California cities.

Suggested by much earlier Schick and Dick test studies by Doull and others[7] made in tropical and temperate areas, it was arranged that antistreptolysin "O" tests would be performed by Dr. Nell Hollinger and her assistants on all our sera collected for Lansing poliomyelitis neutralizing antibodies. A remarkable correlation appeared between the age of development of the two antibodies in all geographic areas included.[9] However, there was only the expected chance occurrence or absence of the two antibodies in individual sera, indicating that the antibody responses measured were due to two different agents. The correlation observed between the age trends of these two antibodies suggested strongly that there were marked immunologic or epidemiologic parallels between streptococcal and poliomyelitic infections, as measured serologically. Certain parallels with diphtherial Schick test findings were also striking.[7]

Since we know that diptherial and possibly streptococcal infections may occur repeatedly at a subclinical level in persons previously infected, and thus lead to an inapparent carrier state in the so-called "immune" individual, we sought information to determine if this might be the case in poliomyelitis. In other words, we posed the question—does poliomyelitis behave like we believe rubeola and varicella do, giving permanent immunity to subclinical as well as to clinical disease, or does it behave more like diphtheria, where Schick negative individuals may become reinfected and serve as inapparent carriers? In pursuing this idea consideration was first centered on the apparent discrepancy between the low proportion of adults and older children known to be free from antibodies and the reported high proportion of virus carriers in this age group found in families where a single clinical case occurred.[13-18] This suggested that the carrier state might occur in immune individuals.

This concept was further supported by a chimpanzee experiment performed by Howe and Bodian in which animals given hyperimmune, specific antiserum developed inapparent infection and the carrier state after feeding on virus, just as did the control chimpanzees who received no immune serum.[19]

We have drawn further indirect evidence from epidemiologic reasoning about the apparent persistence of poliomyelitis virus on the island of Guam, where rubeola, pertussis, epidemic parotitis and other solidly immunizing infections have died out repeatedly and required reintroduction by visitors.[7] Streptococcal and diphtherial infections appear to remain present there and evidence suggests that poliomyelitis must have remained similarly, probably through reinfection of immunes who became inapparent carriers.

Other chimpanzee and baby monkey feeding experiments indicate, on the other hand, that specific immunity to reinfection does occur,[20, 21] but the experiments have not tested

for reinfection except after short periods of time. One may still postulate that this complete immunity lasts for months only, not for years, but the answer is not yet available.

The duration of antibody following infection has been a matter of speculation until recently when a fortunate finding was revealed by Paul.[22] In the sera of a group of Eskimos from Point Barrow, Alaska, he found Lansing type neutralizing antibodies practically absent in those under 20 years of age and present in those above 20 years. He also obtained the history of paralytic poliomyelitis occurring 19 years previously. It is difficult to interpret these findings in any way other than that antibody remains present in infected persons for at least 20 years.

Part of the discussion, to this point, may have appeared to be too much of an immunologic review to be appropriate for a group of pediatricians, but these theoretic concepts must form the basis for any plans to control poliomyelitis, either by quarantine or by immunization procedures. For example, if quarantine of contacts is to be used as a control method, older children and adults could reasonably escape inclusion if, presumably immune, they cannot be carriers by reinfection. However, if immunity does not prevent reinfection, no quarantine would be reasonable that did not extend to adults in intimate household contact with the patient.

Poliomyelitis immunization is receiving serious consideration by certain groups in the United States and immunologic information is accumulating rapidly under the impetus of this interest.

Virus typing has been undertaken and there is good evidence of the general presence of at least three immunologic types of virus in the United States. None of these viruses appears to produce immunity for the others. The search is on for other types and it seems quite possible that others will be found. Any immunization program, therefore, must face the fact that at least three separate immunologic types of virus must be represented in the antigen, or antibodies, to these three in any antiserum to be administered.

Some of the practical barriers to be overcome in active immunization are: (1) Multiplicity of strains, (2) dangers in the administration of live virus, (3) in using an inactivated virus, the possible necessity for annual administration from infancy until death, (4) possible dangers of allergic encephalomyelitis resulting from repeated administration of antigen associated with brain tissue, (5) cost and technical difficulty of producing adequate quantities of antigen by inoculation of monkeys or special tissue cultures and (6) very few children need protection since morbidity rates to paralytic infection are low, yet there is no known method of selecting the susceptibles.

At the San Francisco meeting of the American Academy of Pediatrics we recently reviewed the status of possible passive immunization.[23] After carefully weighing the modest amount of factual data available and discussing many of the possibilities, we concluded that, at the time of a recognized epidemic, passive protection of exposed children or of all children of a highly susceptible age might be practical. Gamma globulin has been shown to have a high concentration of antibody against all three recognized types of virus[24] and it will protect laboratory animals.[23] Whether it will protect man is as yet unknown as is also the dosage required and the duration of the immunity. It would appear on the basis of present evidence to deserve a series of field trials. To determine its effectiveness it would have to be given to every other child in a large population or in a series of small groups in well-controlled, carefully planned experiments.

If the suggestions made earlier in respect to immunity not preventing reinfection should be established as fact, then gamma globulin given during an epidemic, if the dosage given

were not excessive, might prevent serious disease yet not prevent infection after contact. The resultant development of a naturally acquired immunity might be expected to reduce the possibility of developing paralysis in future exposures. Thus, nature's method of protecting older children and adults would not be seriously disturbed by the artificial procedure.

Antibiotic or chemotherapeutic agents, if and when one should become available, may serve as the ultimate and best means to control poliomyelitis. Although there is good basis for hope, no agent is available as yet. Thus, studies on the epidemiology and immunology of this important disease must be continued as one of the logical approaches to eventual development of control measures.

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NEWS AND ANNOUNCEMENTS

The University of Minnesota will present a continuation course in Child Psychiatry for General Physicians and Pediatricians Nov. 26 to Dec. 1, 1951. For further details write George N. Aagard, M.D., Director, Department of Continuation Medical Education, University of Minnesota, The Medical School, Minneapolis 14, Minn.

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THE JACOBI FUND

The Section on Pediatrics of the American Medical Association at the meeting held in June 1951 decided to activate the Jacobi Fund, inactive since World War II.

The Fund had its inception at a meeting of the Section in 1921 for the purpose of defraying the expenses of guest speakers, thereby promoting research and education in the field of pediatrics. It was named the Jacobi Fund to memorialize the name of the "father of American pediatrics," Abraham Jacobi of New York City. Jacobi, a former president of the American Medical Association, was the first chairman of the Section on Diseases of Children in 1880.

With no solicitation of funds for many years the principal of the Jacobi Fund now amounts to $5,532, invested in Government bonds, and the revenue is insufficient to carry out the purpose for which it was created. It is intended to stimulate interest in the Section meetings by inviting guest speakers as well as to reimburse our Director of the Scientific Exhibit and our Delegate to the House of Delegates of the American Medical Association. Both of these positions require a considerable amount of work, time and travel expense and it is unreasonable to continue the practice of having the members who are elected to these positions bear all the travel and hotel expense necessary to carry out the duties of their offices.

It becomes necessary, therefore, to replenish the monies we have spent to re-imburse distinguished guests and to expand our program. We are inviting all pediatricians to make a contribution of 5, 10 or more dollars to the Fund. This is a deductible item on income tax returns. Please make checks payable to the Jacobi Fund and send to Hugh L. Dwyer, M.D., Custodian, 315 Nichols Road, Kansas City 2, Mo.

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Dr. Joseph I. Linde of New Haven, Conn., died on Sept. 15, 1951. He was a fellow of the American Academy of Pediatrics.

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The American Board of Pediatrics announces the following dates for oral examinations: New York City, February 1, 2 and 3, 1952; St. Louis, April, 1952; Washington, D.C., May 3, 4 and 5, 1952; San Francisco, June 1952; Chicago, October 1952; Boston, November 1952.

Written examinations under local Monitors will be held on Friday, January 11, 1952. This is the only written examination which will be given in 1952.

BOOK REVIEWS

GREAT ORMOND STREET JOURNAL, Published for the Board of Management, The Hospital for Sick Children, H. K. Lewis, & Co., Ltd. London, W.C. 1, Price per issue 7s 6d. Net.

This is a new journal in the pediatric field, being the Proceedings of the Hospital for Sick Children, Great Ormond Street, London. The first issue is dated June 1951. The paper cover is in french grey blue with the great seal of the hospital making a very pleasing appearance. The issue consists of 59 pages with illustrations covering 9 individual articles on a variety of subjects. It is a pretentious publication and should find its place in pediatric and hospital libraries everywhere. The publishers deserve credit for their excellent format. PEDIATRICS takes pleasure in welcoming a new publication of such quality.

COURRIER—International Children's Centre, Paris, 2,000 francs per year; Editor: Dr. Raymond Mande.

The Courrier of the International Children's Centre has appeared. The first issue is November 1950. It is a monthly review in French and English published 10 times a year. It contains original articles and informational items in medical and social aspects of childhood for physicians, research workers and other professional groups in this field. It contains also in larger part an analytic bibliography of articles concerning children with classification under numerous headings. It will contain international studies on children's problems and news about the activities of the Centre itself. A microfilm or photostatic service will be available to subscribers. It is unfortunate that the style of the Quarterly Cumulative Index Medicus is not used for references. Maybe the several indexing and bibliographic publications could agree in common on a uniform style for all.

The analyses are sufficient in the general field to be adequate. They are short and sufficiently descriptive for a subject so broad and with such wide coverage of publications.

PLASMA PROTEIN, Symposia on Nutrition of the Robert Gould Research Foundation, edited by John B. Youmans, M.D., Springfield, Ill., Charles C Thomas, Publisher, 1950, $6.50, 352 pp. with 85 figures and 48 tables.

This volume contains 17 separate papers or chapters reporting results of original research and discussions by recognized authorities on all important aspects of the plasma protein problem. Some of the topics discussed which are of special interest to the clinician are those relating to (1) the fractionation and properties of normal human plasma proteins, (2) plasma protein formation in health and in various disease states, (3) effects of various types of diet on plasma protein fabrication, (4) the fate of intravenously administered human plasma proteins in health, in idiopathic hypoproteinemia and in osteoporosis, (5) the mechanism of edema formation in relationship to hypoproteinemia, (6) the relationship of protein metabolism to resistance to infection, (7) the influence of the adrenal cortex on plasma protein formation and utilization and (8) the quantitative immunochemical data concerning antibody-containing serum fractions obtained by salt precipitation, alcohol precipitation or delipidation. A new approach to certain obscure metabolic disorders may, in the opinion of the reviewer, grow out of studies on amino acid antagonists discussed in the Symposium by one author.

Low environmental temperature (45° F.) is reported by another author to be a significant contributing factor in experimental hypoproteinemic edema. One essayist points out the frequently encountered lack of relationship between the level of serum proteins, colloidal osmotic pressure and occurrence or nonoccurrence of edema. These discrepancies with the Law of Starling observed in certain disease states are attributed to certain neglected factors, such as the occurrence in the blood of abnormal proteins of high molecular weight and abnormal alterations in the tissues due to under-nutrition.

The processes of depletion and repletion of both cellular and plasma proteins are thoroughly discussed. In depletion, 30 times as much nitrogen is reported to be lost from body tissues than

from the circulating plasma proteins. Cytoplasmic protein of liver decreases most rapidly. The decrease is associated with reduced liver function. The rate of repletion varies directly with the nutritive value of the protein. A marked imbalance of amino acids can deplete one tissue while building up another. For example, gluten favors formation of plasma proteins but fills other stores inefficiently.

Plasma protein injected intravenously into a normal individual is reported to be completely accounted for by "burning" and by "conversion" of protein to cytoplasm over a period of 4 days. When given by mouth a similar amount of plasma protein is accounted for on the same day by "conversion" and "burning." In certain cases of idiopathic hypoproteinemia it appears that the defect in protein metabolism is not failure to form plasma protein but increased destruction thereof. One report hypothesizes that serum albumin is a precursor to bone matrix. This hypothesis is based on the observation that calcium excretion in a patient with osteoporosis was decreased after injections of serum albumin. After thoroughly reviewing the evidence for and against the claim that resistance to infection is dependent in part upon dietary protein, one eminent author concludes that it plays a major role in this process. The volume can be recommended highly to anyone who is interested in the subject of plasma proteins and protein metabolism.

RECENT ADVANCES IN NUTRITION, Paul R. Cannon, Ph.D., M.D., Lawrence, Kansas, University of Kansas Press, 1950, $2.00, 72 pp.

This book is divided into 3 portions corresponding to the 3 Porter Lectures given by Dr. Cannon at the University of Kansas. The work described was done by a research team at the University of Chicago. In an interesting and easily understood manner the author discusses new advances made in the field of nutrition over the past 2 decades.

The first portion of the monograph is devoted to a brief discussion of earlier data gathered by other investigative groups which contributed to the present work. There is a brief definition of the Rat-Repletion Method of nutrition assay developed by Dr. Cannon and his group. The author goes on to present lucidly many interesting findings concerning protein metabolism and its relationship to ingestion of foodstuffs and the formation by the body of necessary tissue proteins. The criteria used are weight gain, plasma protein formation, antibody formation and rat-repletion.

Emphasized by the experiments described is the importance of the essential amino acids. Equally important, however, are the presence of an adequate caloric intake, vitamins and time relationships of ingestion. All of these details are presented in an easily understood manner using simple bar graphs. To emphasize even further the importance of the essential amino acids and the conditions necessary for their utilization, there is presented some of the pathologic aspects of protein nutrition.

This monograph does not by any means provide a comprehensive contribution to the field of nutrition, but rather contributes to those practitioners who are constantly applying nutritional knowledge into therapeutic measures. It gives an interesting and stimulating view of what might be expected in the field of nutrition in the future and should be of value to pediatricians who are constantly faced with problems of nutrition.